DAVINCI MEDICAL ACADEMY

SUBJECTS IN NUTSHELL FOR EFFECTIVE REVISION

ANATOMY IN NUTSHELL

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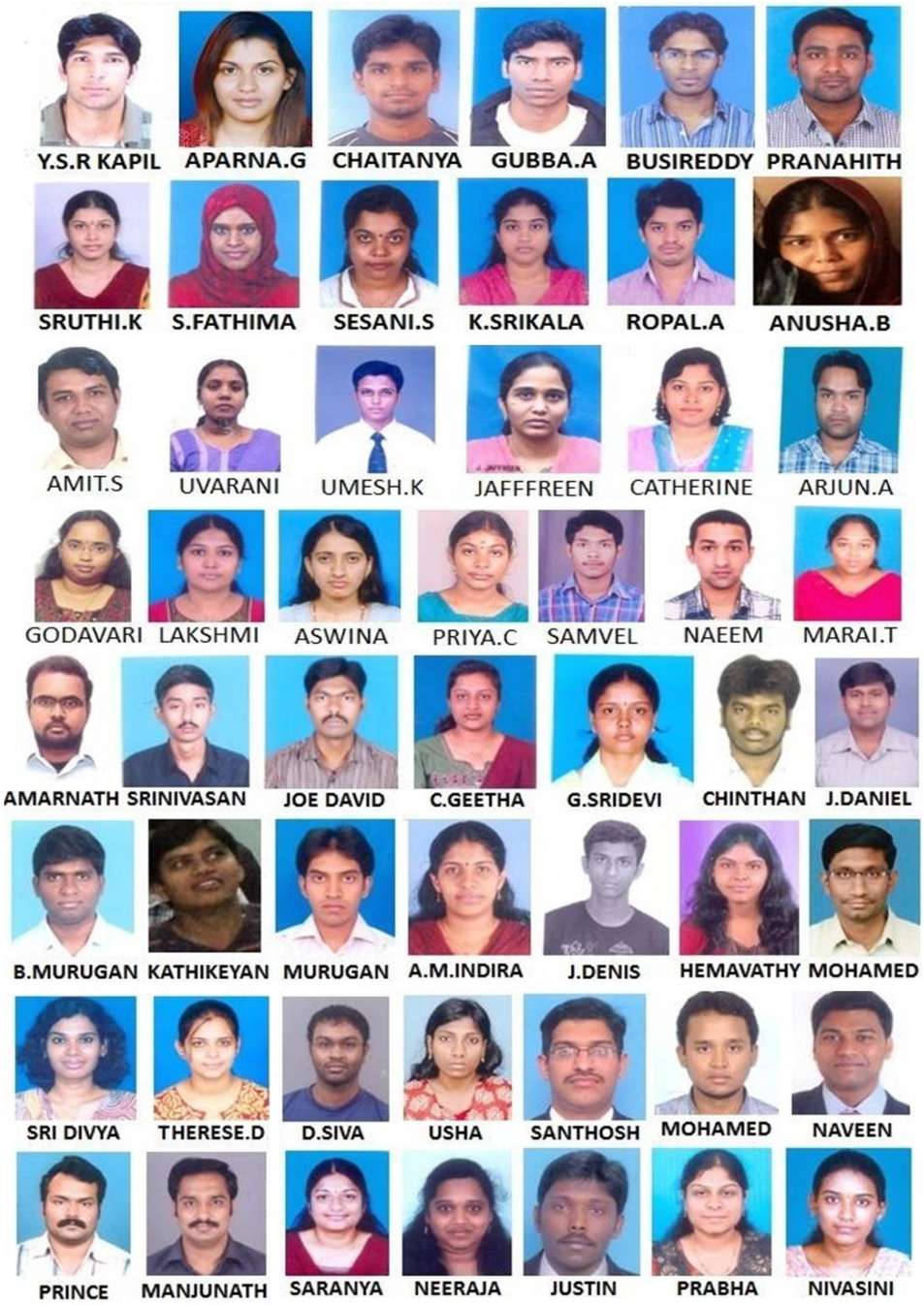
ELITE TEAM OF FACULTY

SOME OF OUR FMGE TOPPERS



DMA'S CORNER OF WISDOM

1- MORPHOLOGICAL CLASSIFICATION OF EPITHELIA

Simple epithelia		
Squamous/pavement	**Cuboidal and Columnar**	**Pseudostratified columnar**
○ Very flattened cells presenting a minimal barrier to the passage of materials, e.g., oxygen, through them. ○ Cytoplasm is very hard to see with LM. ○ The very similar endothelium and mesothelium	○ Cell shape is indicated approximately by the name; most epithelial cells are really polyhedral with many sides or faces. ○ Cells stand one cell high, although their nuclei may lie at slightly different levels. ○ Cells are fastened and sealed at the top of their sides by encircling junctional complexes. ○ Cells have three surfaces: free/luminal, lateral and basal; each may have membrane specializations ○ Note the position and shape of the nucleus, and special locations of organelles and inclusions that also indicate the cell's polarization.	○ Nuclei lie at different levels suggesting stratification, but all cells are in contact with the BL. ○ Two or more cell types are present: short basal, tall columnar.
○ Simple squamous: Bowman`s capsule, lung alveoli	○ Simple cuboidal: kidney tubules ○ Simple columna: gall-bladder, gut, uterus (ciliated)	○ Ppseudostratified columnar: epididymis, trachea (ciliated)

Stratified/compound/layered epithelia		
Stratified squamous	**Keratinized/cornified stratified squamous**	**Transitional/urinary**
○ Many cells thick. ○ Surface cells are flat plates and flake off as squames. ○ Basal-most cells are cuboidal or columnar and divide. ○ Cells above the base become polyhedral and are held together by many desmosomes to resist the abrasive forces on this protective epithelium. ○ Underside of the epithelium is indented by vascular papillae of connective tissue, except in the cornea	○ Similar in its basal and middle layers to 7 ○ Uppermost epithelium has granular cells concerned with forming special, dead cells solidly packed together as a surface keratin layer for greater protection.	○ Several cells thick, but the surface cells are large, rounded, alive and sometimes binucleate, with spare cell membrane in vesicles. ○ No connective tissue papillae indent the epithelium.

Non-epithelial structures sometimes occur within an epithelium	
1. Capillaries - very rarely; only in cochlear stria vascularis. 2. Nerve axons - common in skin, oral mucosa; less common elsewhere. 3. Neural crest derivatives - as melanocytes, and accessory glial-type cells associated with receptors.	4. Lymphocytes - common in gut and airway; less common elsewhere. 5. Langerhans cells - contributors to immune defence in stratified squamous epithelia. 6. Globular leucocytes - a special granular leucocyte of some epithelia.

Devices for attachment	
○ These are used to attach not only epithelial cells but, with some modification, those of the other tissues, e.g. muscle, osteocytes, neurons. To be seen clearly or at all, EM is needed.	
1 Junctional complex of: the girdle-like zonula occludens and zonula adhaerens/belt desmosome, below which is a ring of maculae adhaerentes/ spot desmosomes. Filaments of the terminal web in each cell's apical cytoplasm fasten to the complex. Something of the complex was seen as the terminal bar of LM. 2 Desmosome (the macula/spot/punctate kind of adhaerens attachment): disc-like structures scattered on cell's surface; each is contributed to by membranes of two cells; cytoplasmic tonofilaments (keratin intermediate filaments) converge on and insert into dense subplasmalemmal plaques. There are distinct plaque and desmosomal membrane proteins. 3 Hemi-desmosome: for better adhesion of the basal cell membrane to the basal lamina; includes a plaque and tonofilaments.	4 Gap junction/nexus: where two cells' membranes come closely together with only a 2 nm gap bridged by 'connexons' allowing ions, nucleotides, and amino acids to pass from cell to cell for coupling and coordination of many cells' activities. 5 Tight junction (resembles a zonula occludens but is not always belt-like): outer parts of two cells' membranes are fused together thereby occluding the intercellular cleft. 6 Plication/folding and interdigitation of the adjoining cells' folded membranes. 7 Glycocalyx in the usual 20 nm cleft existing between membranes where specialized attachment are absent. 8 Cell bridges with true cytoplasmic continuity: seen only rarely, e.g., between spermatids. 9 Fascia adhaerens: at intercalated discs of cardiac muscle.

SUPPORT AND NUTRITION
1 The **basement membrane** (BM) seen in LM is the basal lamina, fibrils and connective-tissue ground substances. 2 The **lamina propria** has collagenous and elastic fibres, other matrix materials, fibroblast cells, blood and lymphatic vessels, and wandering defensive cells to protect it and the epithelium.

3 The **nutrition** of epithelial cells is by indirect exchange through the BL and matrix substances with blood in the capillaries of the lamina propria.
4 **Tunica mucosa** (abbreviated to mucosa)/mucous membrane comprises an epithelium, its BL, and the lamina propria, including structures such as glands lying in it.

2 - CELLS OF CONNECTIVE TISSUES

Fibroblast

Young active form	Adult quiescent form
○ Young has abundant, basophilic cytoplasm, with a well-developed Golgi complex and GER for protein and proteoglycan synthesis. ○ Nucleus is ovoid, with weakly staining chromatin granules. ○ The cell is elongated, and often sends out processes to take on a more elongated or stellate form. ○ May in some circumstances (wound repair) take on some smooth-muscle characteristics, and become contractile myofibroblasts→contractures of scar	○ Adult fibroblasts (fibrocytes) have smaller, darker nuclei, and very little cytoplasm. ○ They remain fixed and squashed into a spindle/cigar form amongst the fibres that they formed.

○ **Function** - forming and remodelling collagen, reticular and elastic fibres, and the ground substance

Mesenchymal cell

○ Has a similar appearance to a small, young fibroblast, but is far more multipotential in what cell types it can turn into.
○ Differentiate early in life and thereafter are not present, and fibroblasts or other cells can de- and redifferentiate and become osteoblasts.

Macrophage/histiocyte

○ An ovoid or spheroid cell, which may change its shape while lying alongside fibres, or when extending pseudopodia to move and ingest materials.
○ Nucleus is smaller and more condensed than that of the active fibroblast.
○ Cytoplasm is pale with little GER, but has many lysosomes, when digesting phagocytosed material.
○ Phagocytoses dead cells, cell debris, live and inert foreign bodies & Coordinates the inflammatory response and healing
○ Macrophages may fuse to become foreign-body giant cells with many nuclei, when faced with a large object for digestion.

Macrophage/reticuloendothelial/mononuclear phagocyte system (MPS)

○ Comprises cells related directly to blood monocytes, or derived from the same precursor in marrow.
○ A tentative division of the macrophage-system cells recognizes:

Phagocytic antigen-presenters	Weakly phagocytic APC	Specialized (Some not phagocytic? APC?)
(a) Macrophages of connective tissues and serous cavities. (b) Alveolar macrophages c) Macrophages of lymph nodes, spleen and bone marrow. (d) Kupffer sinusoid-lining cells of liver.	(e) Dendritic and interdigitating reticulum cells of lymphoid tissues. (f) Langerhans cells of epidermis and other epithelia.	(g) Foreign-body giant cells. (h) Microglia cells of CNS. (i) Synovial A cells lining joints. (j) Osteoclasts resorbing bone.

Mast cell

○ A watchdog' cell starting the inflammatory response to noxious intruders.
○ From the German verb, mästen, it meant a `fattened' cell.
○ Spheroid or ovoid with a small central nucleus, and its cytoplasm packed with dense basophilic granules.
Granules give a metachromatic staining reaction with thionine or toluidine blue (reddish-purple colour) because they contain a sulphated polysaccharide - heparin.
○ Mast cells favour positions in CT close to veins (MCt subtype), and at dermal and mucosal interfaces with the hostile environments of the skin, airway, and gut (MCtc subtype).

Fat cell/adipocyte

○ A genuinely fattened cell, initially resembling a fibroblast with a few droplets in the cytoplasm.
○ For the white or yellow unilocular fat seen in adult man, the droplets (mainly glycerides of fatty acids) coalesce and more fat is added,
○ until the nucleus is bulged to one side of a spheroid cell up to 200 µm in diameter, distended by a huge droplet.
○ Cytoplasm, with a Golgi complex, ER and mitochondria, is present as an attenuated peripheral shell.

Plasma cell

○ Many tissues, particularly those lining tracts open to outside the body, are not immunologically virgin, but have been exposed to foreign organisms that have provoked immune responses by local CT plasma cells and lymphocytes. A lamina propria may have many of both and some eosinophils(gut)
○ Plasma cells are ovoid, roughly l0 µm in length, with an eccentrically placed nucleus having its denser chromatin granules clumped regularly around the nuclear membrane (clock-face appearance).
○ Cytoplasm is deeply basophilic from the rich GER, except for a pale central region where the Golgi complex lies.

Reticular/reticulum cells

○ At least three kinds of reticular cell:
- Fibroblastic
- Two phagocytic kinds: interdigitating (T-zone) and dendritic (B-zone: antigen-presenting)

○ The supporting reticular fibres of lymphoid tissues and bone marrow are presumed to be produced by the fibroblastic variety.

Melanophore/CT pigment cell/CT melanocyte

○ A process-bearing cell with melanin pigment granules in its cytoplasm.

○ Proteins synthesized by plasma cells in lymphoid organs reach the plasma as immunoglobulins/ antibodies, inactivating foreign invaders 5 Plasma cells in CT make antibodies for local use(in the airway or gut, to counter toxins and control microbial populations)	○ Found in the skin`s dermis, brain's pia matter and the scleral and choroid coats of the eye.

3 - FIBRES OF CONNECTIVE TISSUES

Collagen fibres

Fibres	4 Collagen types
○ Fibres are long, wavy or straight, and colourless. ○ They have great tensile strength and resistance to stretching, whilst retaining considerable flexibility. ○ Fibres are made up of finer fibrils packed together.	○ 4 Of the twenty plus types, some important ones are: • Type I in bone, fibrocartilage, and established soft connective tissues • Type III in these same tissues as embryonic or reparative forerunners (and as a minor mature component) • Type II in hyaline cartilage • Type IV in basement membranes • Type VII to anchor BMs, and Type VIII from endothelium lining vessels.

Reticular fibres	Elastic fibres
○ Collagen fibres, running parallel to one another, do not join up with others running differently. Thus reticular fibres are an immature, fine kind of collagen fibre, mostly of **type III collagen**. ○ Such an arrangement is seen, however, with reticular fibres, which form a network or reticulum. ○ Reticular fibres stain black with reduced silver methods, hence their other names - argyrophil or argentophil. H and E and some trichrome stains leave them unstained. ○ They persist into the adult in several organs, where a fine fibrous support is needed that does not interfere with a close relation between fixed cells and blood or lymph/ endocrine glands. ○ Reticular fibres fasten to the underside of basal laminae of epithelia and endothelium, and bind and secure muscle and nerve fibres, using their external laminae.	○ May be fine, single and branching in areolar CT, or thick and parallel in elastic ligaments. ○ Walls of blood vessels have incomplete elastic membranes. ○ The elastic nature of the fibres is shown by the spiralling and kinking of their recoiled broken ends, in spread preparations. ○ Elastic fibres and membranes, if thick, stain pink with eosin, or red with Masson's method; otherwise, they remain unseen, unless elastic stains: orcein or Verhoeff's, are used. ○ In bulk, unstained, they appear yellow to the naked eye.

4 - GROUND SUBSTANCES

○ **Location** - in interstitial/tissue spaces, cartilage and bone matrices, under basal laminae, on and between CT fibres. Ground substance(s) is the extracellular matrix, less the fibrous and fibrillar elements.
○ **Nature** - large negatively charged proteoglycan molecules (polyanionic macromolecules) bind to a varying degree water, electrolytes, and other macromolecules, such as collagen, and the glycoproteins, fibronectin and tenascin.

Proteoglycan varieties

	Staining
○ Dependent on the specific sugars, and the sites of sulphation, if any: • Hyaluronate - soft CT; synovial fluid; vitreous humour • Dermatan sulphate (chondroitin B) - skin and corneal CT • Keratan suphate - cartilage matrix • Chondroitin-4-sulphate (A) - cartilage matrix • Chondroitin-6-sulphate (C) - cartilage matrix • Heparin (also sulphated) - granules of mast cell and basophil.	○ Failure of counter ions to neutralize all anions leaves regions of high negative charge density. ○ If the proteoglycan is prevented from dissolving out, its reactions are: • Basophilic with basic stains: in hyaline cartilage • Positive with Alcian blue and Hale's iron • Metachromatic with toluidine blue

Fibronectin	Tenascin
○ Forms of the glycoprotein, fibronectin, occur in CT matrices, basal laminae and blood plasma. ○ Fibronectin is a multiple adhesive, since various domains of the molecule bind glycosaminoglycans, collagen, fibrin, and some cells. ○ Made by fibroblasts and available from blood, it helps in the scaffold-building, and cellular migrations and attachments: embryogenesis and wound repair.	○ Tenascin shares some structure with fibronectin, but plays its part more during development: sites of epithelial-mesenchymal interaction. ○ It reappears in malignant tumours. ○ Tenascin and decorin are respectively glycoprotein and proteoglycan examples.

Non-collagenous glycoproteins of connective tissues include: Fibronectin, Tenascin, Thrombospondin, Bone sialoprotein/BSPII, Osteopontin/BSPI, Osteonectin/Bone Gla protein, Cartilage-matrix protein, Alkaline phosphatase, Chondronectin, and Fibrillin.

5 - TYPES OF CONNECTIVE TISSUES

Areolar tissue	White adipose tissue
○ Loose textured with a mixture of all cell and fibre types (but seldom pigmented cells).	○ Comprises primarily fat cells enclosed in basal lamina, and held on a framework of reticular fibres in association with

- Rich in ground substances which fill the spaces or areolae, and confer physical properties and control transport.
- Locations: the lamina propria of the gut, under the skin, around joints, muscles and some viscera, and other sites needing some freedom of movement; the eye's choroid coat serving a more nutritive role also has pigment cells.
- Serous membranes are similar to areolar tissue but also have a layer of simple squamous mesothelium
- Milky spots on serous membranes are dense accumulations of the macrophages and lymphocytes present to protect serous body cavities.

many blood capillaries.

- Fibrous CT encloses the tissue, subdividing it with septa.
- Found subcutaneously in the hypodermis (in the child, a panniculosus adiposus), and in the mesentery, omentum, and retroperitoneal area.
- Padding fat in palmar, plantar and intraorbital sites is not so freely available as an energy store, and can survive starvation.
- Adipose deposits in the hips, buttocks, and breasts are especially under the control of female sex hormones, but many hormones control fat metabolism.
- Functions: energy store; insulation; padding; steroid conversions.

Brown adipose tissue

- Cells have many separate (multilocular) fat droplets, relatively more cytoplasm, and are smaller than white fat cells.
- Found around the thorax and kidneys of animals naturally exposed to severe cold, particularly hibernators.
- Brown fat is a thermogenic organ providing a prompt and direct source of heat to maintain the temperature of vital organs.
- Seen in the human newborn; in adults BAT is detectable after adrenergic stimulation.
- Brown fat might dissipate surplus energy from overeating.

Reticular tissue

- Has the reticular fibre as the supporting fibre, and phagocytic fixed macrophages.
- The fibres are made by some of the stellate reticular cells acting as fibroblasts.
- Reticular tissue also contains parenchymal cells (the main working cells) held by the fibres: hepatocytes or lymphocytes.

Elastic tissue

- Elastic fibres or membranes are the predominant element.
  The fibres may be:
  - thick or very thick (10-15 μm) and orderly as in the elastic ligaments: ligamentum nuchae (in the neck of heavy-headed grazing animals), vertebral ligamentum flavum, penile suspensory ligament, and in the vocal chords
  - finer and mixed with membranes in elastic arteries. The lung and airway also have many elastic fibres
- In the ligaments, elastic fibres are formed by fibroblasts and held together by reticular fibres, proteoglycan, and glycoproteins.

Dense fibrous (collagenous) tissue

- **Two kinds:**
- **Regular:** tendon, ligament, aponeurosis, fascia, with collagen fibres oriented to take stress principally in one direction. (The dense corneal stroma has very orderly collagen for transparency as well as strength.)
- **Irregular:** dermis, organ capsules, periosteum, perichondrium, epitendineum, with irregular, interwoven bundles of collagen.

Loose fibrous (collagenous) tissue

- Have fibroblasts and collagen fibres as the principal elements, reticular and elastic fibres and other cells are present to a lesser degree, together with blood and lymphatic vessels and nerves.
- An example of a loose fibrous tissue is the lamina propria of the urinary bladder, looser than dermis, denser than that of the gut.

Mucous/mucoid/primitive connective tissue

- Very rich in proteoglycans and water, has some fine collagen fibres and widely separated young fibroblasts.
- As Wharton's jelly of the umbilical cord it encloses and cushions the vessels; the ocular vitreous and young dental pulp also fit tolerably well in this class.

6 – CARTILAGE

- CT to resist compression, and provide modest rigidity with flexibility consists of chondrocytes that produce a firm resilient matrix of ground substances, and fibres or fibrils.

HYALINE CARTILAGE

- Looking hyaline/translucent (glass-like) to the unaided eye.
- Most surfaces except articular ones are covered by a nutritive perichondrium/capsule with collagen and elastic fibres, fibroblasts and blood vessels.
- **Matrix** apparently amorphous with HE staining in LM containing proteoglycans, type II collagen and glycoproteins.
- **Chondrocytes** or cartilage cells are large and rounded, each lying in a space - lacuna - enclosed by matrix & grouped in nests of 2, 4, or 6 as a result of mitoses and restricted cellular movement.
- **Growth** occurs in two ways:
  - Appositional/perichondral by the recruitment of fresh cells
  - Interstitial by the mitotic division and deposition of matrix around by chondrocytes
- **Territories**:

ELASTIC/YELLOW CARTILAGE

- More opaque and flexible than the hyaline kind, but the cells are similar in appearance and distribution; and it occurs as separate pieces with a perichondrium.
- Matrix is permeated by many elastic fibres that can be selectively stained by stains such as orcein or Verhoeff's.
- The matrix is not prone to degeneration and calcification.
- **Location:** external ear, pharyngotympanic tube, epiglottis, and some laryngeal and bronchiolar cartilages.

FIBROCARTILAGE

- Rather disorderly matrix with many thick collagen

- Chondron - the chondrocyte and the pericellular matrix immediately around it;
- Proteoglycan-rich territorial matrix outside the chondron;
- Interterritorial matrix, lying between the territorial matrices

○ **Nutrition:**
- Cartilage is avascular and no blood vessels serve the matrix directly, but cartilage canals may carry vessels

○ **Location:**
- Articular surface of most synovial joints; costal cartilages; nasal and respiratory tract cartilages; basis of most of the fetal skeleton; fracture callus,

fibres, amongst which are dispersed only a few chondrocytes in lacunae.
○ The matrix gives the staining reaction of collagen, mostly type I, except for close around the cells where proteoglycans are abundant.
○ Lacks a perichondrium and is not seen as discrete pieces; rather it is a strong tension-resistant, but flexible.
○ **Location:** intervertebral disc's annulus fibrosus; pubic symphysis; femoral ligamentum teres; many tendon insertions into bone; and the articular surface of some joints, e.g., temporomandibular.

7- BONE

○ Bone is a hard CT with cells, osteocytes, in much matrix, and serves for support, attachment, leverage, protection and mineral storage.

CLASSIFICATIONS OF BONE

○ Based on the size of the spaces within the bone, and its trabecular (lattice-like) or dense nature:
(a) Cancellous/spongy/trabecular
(b) Compact/dense

○ Based on the presence or absence of lamellae (layers) and osteons/Haversian systems:
(a) Woven/primitive
(b) Lamellar/Haversian

○ Woven bone's matrix has disorderly fibrils, whereas in lamellar bone the fibrils of a lamella share a predominant orientation.
○ Note that a particular bone will have areas of woven and lamellar bone, depending on how far remodelling has involved all regions.

HAVERSIAN BONE

○ Haversian system is roughly cylindrical and arranged around one or two small vessels in a central Haversian canal.
○ Osteocytes and bone lamellae making up the system are disposed in 4-20 concentric rings centred on the canal.
○ A lamella is the territory formed and maintained by the osteocytes lying in a ring when seen in a cross-section.
○ Haversian canals branch and join up with others. Their vessels originally entered the bone from the periosteum or marrow via Volkmann's canals, around which osteocytes are not especially ordered.

MATURE HUMAN BONE

○ **Periosteum of dense CT divisible into:**
(a) an external fibrous layer of collagen and elastic fibres, fibroblasts, other cells, vessels and nerves; and
(b) an inner cambial layer of bone cells, mostly resting osteoblasts.
○ **Dense cortical bone**:
(a) external circumferential/basic lamellae lie outside;
(b) main thickness with many osteons of various generations (primary+secondary); interstitial lamellae fill the chinks between osteons and are lamellae of earlier osteons that have been spared total ersion.
(d) endosteal/internal circumferential lamellae lie to the inside.
○ **Cancellous medullary bone:** whose trabeculae are lined by a thin cellular endosteum and have some lamellae, but can be sustained by marrow blood vessels without the need for Haversian canals.
○ **Marrow cavities** lie between trabeculae, inside the tubular shaft, or in the diploic spaces of flat skull bones.

BONE CELLS

Osteoblast

○ Lies on the surfaces of bone, in a one-cell thick layer, as most of the endosteum and inner periosteum.
○ May be in two states:
(a) active, forming bone matrix
(b) resting or bone-maintaining
○ Forms the collagen, glycoproteins, and proteoglycans of the matrix, and controls the deposition of mineral crystals on the fibrils.

Osteocyte

○ Osteoblast becomes an osteocyte by forming matrix around itself and becoming buried or immured.
○ Young osteocyte thus resembles an active osteoblast; older ones have smaller, flattened bodies.
○ Processes extending from the body down the canaliculi are not visible by LM
○ The mature osteocyte is involved in maintaining the matrix of its territory.
○ Lacunae empty of osteocytes indicate dead bone.

Osteoclast

○ Large, multinucleated cell, with a pale acidophilic cytoplasm.
○ Lies on the surface of bone, often in an eaten-out hollow - Howship`s lacuna.
○ Cell surface is attached to the bone by podosomes to create a sealed compartment against the bone, in which the moving long cell processes of the ruffled border can agitate the resorbing - bone-destroying - materials.
○ Cytoplasm has vacuoles and lysosomes, since the mechanism of bone resorption is partly an enzymatic digestion

HISTOLOGICAL METHODS FOR BONE

○ **Ground sections** with the mineral present are made by sawing out a slice of bone (or tooth) and grinding it thinner. They

show osteons, lacunae and canaliculi, but these hold air or debris and no longer cells.

- **Decalcified sections** are cut from bone imbedded in the usual way after removal of the mineral by dilute acids or chelating agents. Cells and the organic matrix remain. Eosin and selective collagen stains reveal the dense collagenous matrix, but individual fibrils and canaliculi are not seen unless special stains are used.
- **Mineral density** can be studied by the magnified X-ray image of microradiography in ground sections or microtome-cut sections of plastic-imbedded undecalcified bone obtained by biopsy.
- **Electron microscopy** of such plastic sections gives a comprehensive view of mineral, collagen, and cells, and their interactions.
- **Vital labelling**, with the fluorescing tetracyclines, alizarin red (in madder), or the radioactive isotopes, ^{45}Ca or ^{31}P, given at known times, permits the amount and sites of new bone formation, and its patterns of deposition and resorption to be identified, and related to bone diseases or experimental manipulations.

8- JOINTS

Diarthrosis

- **Articular cartilage,** usually hyaline, covers the moving bone ends, and is nourished and lubricated by synovial fluid.
- **Joint capsule** of dense irregular fibrous CT, continuous with the periostea, encloses a joint space for synovial fluid.
- **Synovial membrane:** lines the capsule; a cellular layer, with macrophage (A/M) and fibroblastic (B/F) cells, lies on a loose vascular CT, sometimes thrown up into folds, synovial villi.
- The cells make lubricating hyaluronic acid and glycoproteins, and determine the nature of the cartilage-sustaining synovial fluid.

9- MUSCLES

SKELETAL MUSCLES

CT sheaths and subdivisions	Individual skeletal muscle fibre
○ CT epimysium encloses the whole muscle; ○ CT perimysium encloses each fasciculus (bundle) of fibres; ○ CT endomysium encloses each muscle fibre.	○ Outside lies a connective tissue endomysium with some fibroblasts, collagen fibrils, and capillaries. ○ Cell membrane is the sarcolemma + directly under the sarcolemma lie elongated nuclei. ○ The cell, as another product of cell fusion, is multinucleated. ○ In one place, the sarcolemma is modified to take a nerve fibre's terminal motor-end-plate/ myoneural junction ○ Fibre is large and cylindrical.

CARDIAC MUSCLE COMPARED WITH SKELETAL	SMOOTH MUSCLE
○ Cross-banded, with the same repetitive sequence ○ Intercalated discs mark a strong end-to-end cell connection. The muscle thus pulls upon itself during contraction. ○ Each cell has only one or two nuclei lying centrally, elongated, but with blunt ends. ○ Fibres are narrower. ○ Fibres branch and anastomose and, until intercalated discs were discerned using EM, the muscle was believed to be syncytial - one huge cell. ○ EM shows the intercalated discs to be extensive, interdigitated cell junctions with gap junctions, fasciae adhaerentes, where the myofibrils attach, and desmosomes. ○ Mitochondria are more numerous. ○ There is less CT. ○ Cardiac myofilaments are not clearly aggregated into myofibrils.	○ Fibres are spindle-shaped (fusiform) with one, central, cigar-shaped nucleus. ○ Fibres show no cross-banding, but have many fine filaments. Cells are firmly attached by gap junctions, and elsewhere by glycoprotein external laminae (like basal lamina). ○ Fibres are usually packed to form a sheet or bundle. Reticular fibres enfold the muscle fibres, assist in holding them together and carry blood vessels, and fine autonomic nerve fibres going to inconspicuous myoneural junctions. ○ The nuclei may be wrinkled in the contracted state. Peripheral vesicles are part of a vesicular and tubular Ca^{2+}-holding sarcoplasmic reticulum. These organelles, and inward protrusions of cell membrane - caveolae - function similarly to the better-defined SR and T-tubules of striated muscle. ○ Myoepithelial cells, wrapped around glandular secretory or duct cells, have contractile processes resembling smooth muscle cells. ○ Vascular smooth muscle cells also can make elastin and collagen during development.

TENDON

- **Tendon** is composed of:
  (a) many bundles of dense, regular, collagen fibres with
  (b) flattened tendon cells (fibroblasts) between them;
  (c) each bundle is loosely bound in a CT sheet - endotendineum;
  (d) peritendinial CT, bearing vessels and nerves, encloses several primary units as one fasciculus; and
  (e) a thick sheath - epitendineum - wraps around the whole tendon of several fasciculi.

10- NEURONS

Shape

- Neurons are characterized by having long processes extending from a cell body/soma. One of these is the axon transmitting information; the others are receptive dendrites.

- Unipolar have one process, e.g., neuroblast.
- Pseudounipolar have one process branching into two a short way from the cell soma, e.g., dorsal-root ganglion cell.
- Bipolar have two processes, e.g., bipolar cell of the retina.
- Multipolar have many processes. Shapes include:
  (a) stellate or star-like,
  (b) pyramidal with apical and basal dendrites, or
  (c) Purkinje with a plump body tapering to an espalier-oriented dendritic tree.

Nerve cell structure

Soma	Dendrites
○ Contains a large central nucleus with much sap, but little visible chromatin. The nucleolus is prominent because the neuron has to synthesize organelles and much cytoplasm to fill its long processes. ○ Around the nucleus is the perikaryon with: (a) Nissl bodies/granules - basophilic, cytoplasmic structures are concentrations of granular ER. (b) Neurofilaments - a variety of intermediate filaments aggregated into neurofibrils visible in the cytoplasm after silver impregnations. (c) Surrounding the nucleus are elements of the Golgi apparatus, mitochondria, lysosomes, and microtubules. Actin filaments move vesicles in the zone directly under the neuron's plasmalemma. (d) Pigment is sometimes present, e.g., melanin in substantia nigra neurons, and lipofuscin in old neurons. (e) Cell membrane has specialized receptive areas, the subsynaptic membranes of synapses.	(a) Contain mitochondria, microtubules, and granular ER. (b) Membranes have receptive subsynaptic membrane areas. (c) Some dendrites have spine-like side processes, also receptive, (d) Dendrites integrate the excitatory influences along them, and modify their responses and morphology in learning.

Nerve fibre (includes the axon and its myelin sheath).

(a) Contains axoplasm flowing centrifugally from the somatic starting-point of the axon - the axon hillock.
(b) Has mitochondria, neurofilaments, microtubules, travelling vesicles, and, in some neurons, secretion droplets, in the axoplasm.
(c) Membrane of the tube is the axolemma, swelling out into a bag at its terminal/synapse which holds vesicles/microvesicles. (The axon is also termed the axis cylinder.)
(d) Myelin sheath of lipoprotein around the axolemma.
(e) EM reveals myelin to have lamellae with alternate dark (major dense) and light (intraperiod) lines, apparently concentric around the axon.

11- CENTRAL NERVOUS SYSTEM

BRAIN BOUNDARIES

- The brain, spinal cord and optic nerves are enclosed in vascular connective tissue sheaths - the meninges - and protected by bone.

Meninges	Ependyma and choroid plexus	Blood-brain barrier
○ **Dura mater - (pachymeninx) -** dense fibrous CT; osteoblastic outside (skull), or mesothelial facing the epidural space (spine); specialized layer of dural fibroblasts attaches dura to arachnoid. ○ **Arachnoid complex -** apposed to the dura is a layer of well attached cells, several cells thick; between this layer and the pia are open subarachnoid spaces, crossed by trabeculae of collagen, clad in other arachnoid cells, and supporting the vessels. ○ **Pia mater -** thin cellular, vascular and collagenous layer, adherent to the BL of the nervous tissue. (Arachnoid and pia comprise the leptomeninges.)	○ Ependymal epithelium lining the ventricular cavities and canals of the CNS is simple, columnar or cuboidal. ○ In regions of each ventricle, tufts of blood vessels (mainly fenestrated capillaries) project out from the pia, and are covered by a loose CT coat, then a layer of cuboidal ependymal cells on a BL.	○ The blood capillaries serving the brain tissue have a characteristic structure of unfenestrated endothelial cells held together by tight/occluding junctions on a thick basal lamina, whose outer surface is enclosed by glial cell processes (astrocytes pedicles).

GLIAL CELLS

- **Protoplasmic astrocytes:** large, star-shaped with many processes, some of which attach pedicels/pedicles/sucker-feet to blood vessels or the basal lamina under the pia mater & common in grey matter.
- **Fibrous astrocytes:** similar to protoplasmic astrocytes, but have more filaments and glycogen, and lie in the white matter.
- **Oligodendrocytes/oligodendroglia:** plump cell body with fairly dense cytoplasm and a darker nucleus and fewer, shorter processes than an astrocyte; common in white matter, but some are perineuronal
- **Peripheral glia:** satellite cells and Schwann cells may be roughly equated with oligodendrocytes by function. Peripheral glia in the gut autonomic system - enteric glia - are more like astrocytes.
- **Olfactory ensheathing cells** enwrap the unmyelinated axons of the olfactory

○ **Microglia:** (a) derived from mesenchyme via bone marrow; (b) potentially phagocytic; (c) dispersed throughout the brain; (d) a small elongated cell with many short processes and a dark nucleus.(phagocytic as a reactive microglial cell→Gitter cell) ○ **Ependymal cells:** lining ventricles, and covering the choroid plexus.	nerve bundles, and may provide favourable cues for axonal regeneration. ○ **Specialized central glia:** Müller astrocytes of the retina, pituitary-gland pituicytes, and periventricular tanycytes extending away from the ventricles.

12- SPECIAL FEATURES OF BRAIN REGIONS

Spinal cord	
○ Enclosed in CT meninges with pia extending in at the ventral fissure with the anterior spinal artery. ○ The ependyma-lined central canal lies centrally. Surrounding the canal in a butterfly shape is grey matter (grey to the naked eye when fresh and unstained). ○ Horns of grey matter partly separate three columns of white matter: dorsal (posterior), lateral, and ventral (anterior) columns. ○ White matter is composed of nerve fibres, many thickly myelinated, running mainly up or down the cord. Generally, fibres projecting to or from a particular brain region run together in a tract. ○ Grey matter has groups of multipolar nerve cell bodies, nerve fibres entering and leaving the grey matter, and preterminal fibre branches (poorly myelinated, hence the grey colour in the fresh, unstained cord).	○ Glial cells and blood vessels are in both white and grey matter. Grey matter is more vascular. The oligodendrocyte is the principal glial cell of white matter. ○ Roots of nerve fibres enter the cord on the dorsal sides; other roots leave on the ventral sides. ○ Substantia gelatinosa lies at the extreme margin of the dorsal horn of grey matter. ○ The multipolar neurons include: motoneurons, whose axons pass out of the cord to join peripheral nerves and serve skeletal muscles; and short-axoned interneuron/ Renshaw cells.

Cerebellar cortex	**Cerebral cortex**
1- Molecular layer (cell processes, but few cells). 2-Purkinje cell layer. 3-Granule cell layer (densely packed small neurons) (underlying white matter).	l- Molecular layer. ○ Layers 2, 3, 4, 5, 6 with varying proportions of stellate, fusiform and small, medium, and large pyramidal cells (white matter).

Brain stem

(a) Resembles the spinal cord in having nerve cell bodies grouped in nuclei and nerve fibres in tracts.
(b) Some special nuclei of the brain stem and hypothalamus are:
(i) The reticular formation is an extensive system of groups of neurons serving many vital tasks, but whose nuclear organization is hard to discern.
(ii) Neurons of the substantia nigra contain melanin pigment and dopamine.
(iii) Certain hypothalamic nuclei have neurosecretory neurons.

13- PERIPHERAL NERVOUS SYSTEM

○ Connected to the brain by cranial nerves or to the cord by roots combining to form nerves are sensory, relay and effector structures, which send raw sensory data to the central nervous system and receive from it and carry out its instructions.

PERIPHERAL NERVE

Nerves fibres present may be:	**Connective tissue wrappings**
1 centripetal sensory fibres 2 centrifugal motor fibres to skeletal muscle, 3 centrifugal autonomic fibres to glands, and smooth muscles.	1 Epineurium around the whole nerve trunk with blood and lymphatic vessels (vasa nervorum), collagen and fibroblasts, and fat cells. 2 Perineurium around each fasciculus of nerve fibres: the site of the blood-nerve barrier. Perineurial cells are tightly attached. 3 Endoneurium around each individual myelinated nerve fibre, but separated from its Schwann cells by a basal lamina.

Cross-section of nerve in LM shows:	**Single nerve fibre**
1 Close-to-round shape with no lumen; CT coat and divisions. 2 Nuclei of Schwann cells, fibroblasts and a few capillaries. 3 Axons and some remnant of myelin (so-called neurokeratin) around them (with H & 4 brownish-black rings (myelin with an unstained axon within each) (osmium tetroxide treatment). 5 The eosin of H & E shows the collagen of epi- and perineurium, which remain very pale yellow with osmium. Osmium tetroxide will, however, show intensely black the fat in the adipocytes, usually present in epineurium.	○ Single fibres that have branched off from nerves to pass to and enter some kind of end-organ remain unseen unless special techniques are used, although the CT capsule and supporting cells of the end-organ are usually discernible with HE staining. ○ The fibre-revealing techniques are EM, silver impregnation, or histochemical ones for cholinesterase, neuropeptides, and catecholamines.

GANGLIA	
Spinal/dorsal root ganglion (no synapse involved)	**Autonomic ganglion (compared with a spinal ganglion)**
1 Has a collagenous connective tissue investment. 2 Many bundles of thick, myelinated, nerve fibres separate 3 groups of large, round-bodied nerve cells. 4 Each neuron has a thin CT capsule like an endoneurium. 5 Between capsule and neuron is a layer of small satellite cells of a glial nature. 6 Neuron has only one process (not a dendrite) branching into two near to the soma. The thinner axon runs centrally via a dorsal root into the spinal cord, the thicker runs peripherally to a nervous receptor.	1 Fewer myelinated fibres are present. 2 Neurons and fibres are interspersed. 3 Neurons are smaller and have dendrites, with preganglionic fibres synapsing upon them. 4 Many of the neurons' own axons (post-ganglionic fibres) are unmyelinated. 5 In a cross-sectional view, several unmyelinated fibres share one Schwann cell, lying in many deep invaginations of its membrane. In the gut, enteric glia take the place of Schwann cells.

14- CVS

Blood capillaries	
1 Very numerous, anastomosing, delicate tubes of diameter 7-9 µm. 2 Total cross-sectional area of the capillary bed is very great, thus blood flows slowly under low pressure. 3 Wall is made up of curved, thin, plate-like endothelial cells lying on a BL and oriented with the tube's long axis. 4 **Type I** unfenestrated capillaries have complete endothelial cells, e.g., in muscle and skin: 5 **Type II** capillaries have endothelial cells with fenestrations/pores through them (not between them), e.g., in kidney and choroid plexus. 6 Endothelial cells have serrated margins where they attach by adhaerens and tight junctions to each other, tight/occluding junctions predominate where more of a barrier is needed, e.g., in the brain. Continuous capillaries have no gaps between the endothelial cells, in contrast to discontinuous capillaries.	6 Transport is controlled by the cells, with diffusion and facilitated transport for small molecules, and transcytotic vesicles or passage through the pores for larger materials. 7 Some capillaries have the occasional pericapillary cell - pericyte - imbedded within the BL, perhaps playing a contractile role. 8 Show transitions at both ends: to arterioles (by acquiring smooth muscle cells), or venules (by widening and taking on more collagen fibrils).

Sinusoids	Sinusoidal capillaries
1 Have wider, more irregular lumens than capillaries. 2 Some of the lining cells are phagocytic. 3 Basal lamina may deficient or absent so that lining endothelial and phagocytic cells lie directly on reticular fibres and other cells, as in the liver.	2 Have wide irregular lumens and a continuous, but fenestrated, non-phagocytic lining 2 are the usual smallest vessel in endocrine tissue.

Arteries	
○ **Have three main layers composed of several tissues:** ○ **Tunica intima** (a) Endothelial lining on a BL (b) Subendothelial CT (c) Internal elastic lamina (fenestrated) ○ **Tunica media** (d) Smooth muscle cells (tightly spiralling or 'circular') (e) Sparse reticular and elastic fibres ○ **Tunica adventitia** (f) External elastic lamina (interrupted) (g) Collagenous and elastic CT (mostly longitudinal) ○ Arterioles, less than 0.5 mm wide, have (a),(c),(d),(e) and (g) of the above. Small and medium-sized arteries (muscular/distributing) have all elements.	**Large arteries (elastic) differ significantly:** ○ **Tunica intima** (a) Endothelium on a BL (b) Subendothelial CT (c) Innermost fenestrated elastic lamina ○ **Tunica media** (d) Many fenestrated elastic laminae interspersed with (e) smooth muscle cells and collagen fibres ○ **Tunica adventitia** (f) Collagenous CT with vessels and nerves
○ The larger arteries and veins have nutrient vessels and nerves (of vessels) in the adventitia **- vasa vasorum and nervi vasorum.**	

Veins	
○ Venules have an endothelial lining, BL and a collagenous outer sheath. Pericytes are numerous. The wall is thin enough to permit transport through it. ○ White blood cells can squeeze between endothelial cells (transmigration/ diapedesis) and escape into the tissues. Lymphocytes may migrate actually through the interior of the endothelial cell. ○ Emperipolesis is the migration of a cell into (and out of) another cell, while remaining intact: high endothelial cells, megakaryocytes, and thymic epithelio-reticular cells are hosts for such activity	○ Small veins acquire an additional thin media of smooth muscle and a thicker adventitia of collagen and elastic fibres. ○ No distinct elastic laminae are seen, but sparse elastic networks are found throughout the wall. ○ Many veins have valves - leaf-like projections of the intima, usually in a bicuspid form. ○ Large veins (e.g., vena cava) have bundled longitudinal smooth muscle in the CT adventitia and intima, whilst the media is thin or absent.

Comparison between a vein and its companion muscular artery			
○ Both are tubes lined by endothelium and may contain RBCs.			
Artery		**Vein**	
(a) Shape less deformed (b) Thick wall (c) Intima crinkled	(d) Three distinct layers (media prominent) (e) Internal elastic lamina	(a) Flattened (b) Thin wall (c) Intima smooth	(d) Layering indistinct (media weak) (e) No internal elastic lamina
Exceptional vascular structures			
1 Cerebral, retinal and osseous veins have no valves and no media. Veins in general are very variable in their structure. 2 Cerebral arteries are thin walled and have no external elastic layer. 3 Umbilical vein is very muscular; and the umbilical arteries have little elastic, and a media with distinct longitudinal and circular muscle layers. 4 Arterial intimal cushions are present in arteries to erectile tissue, kidneys, etc. 5 Some vessels have a high protruding endothelium, e.g., fetal stem arteries.			

Heart wall`s three layers	
Endocardium (innermost)	**Myocardium**
(a) Lined by endothelium on a basal lamina. (b) Subendothelial layer of collagenous and elastic fibres, fibroblasts and some smooth muscle cells. (c) Subendocardial layer of CT with blood and lymphatic vessels, nerve fibres, and Purkinje fibres of the heart's conducting system. A layer worth calling a subendocardium is not everywhere present.	(a) Cardiac muscle fibres, bundled and wound in spiralling sheets, thickest in the left ventricle, thinnest in the atria. (b) Blood vessels and lymphatics and fine CT.
Epicardium (visceral pericardium) and subepicardium	**Pericardium (parietal)**
(a) Outer mesothelial sheet and BL on (b) loose subepicardial CT of fat cells and collagen fibres with (c) blood vessels (coronary), lymphatics and nerves to the heart nodes.	○ CT membrane of fibres supporting a mesothelium. This faces the epicardium across the pericardial cavity containing a small amount of lubricating fluid.
Cardiac skeleton of dense fibrous CT, with a tendency to turn into fibrocartilage.	
Heart valves	
Atrio-ventricular valves	**Semi-lunar valves**
... (a) Leaflets are covered with endothelium on a ... (b) core of dense CT fused to the supporting annulus. ... (c) Cords of CT (chordae tendineae) connect the valve to ... (d) the papillary muscles in the ventricular wall.	... (a) Deploy three leaflets. ... (b) Thinner than the atrio-ventricular valves. ... (c) Lack chordae tendineae. ... (d) Fibrous core enlarges to the nodule of Arantius at the free margin.
Impulse-conducting system	
1 Sino-atrial node of thin, modified, cardiac muscle fibres, influenced by parasympathetic (ganglionic neurons are found in the heart) and sympathetic autonomic nerve fibres, initiates contraction (pacemaker). 2 Contraction spreads through the atrial myocardium to the 3 atrio-ventricular node (Tawara's) consisting of a tangled plexus of modified cardiac fibres in the medial wall of the right atrium.	4 These fibres enlarge into Purkinje fibres and continue through the septal CT as the bundle of His, which then branches. 5 Purkinje fibres are rich in sarcoplasm and glycogen, but poor in myofilaments. They lack T-tubules, and are connected by intermediary transitional cells with ordinary myocardial fibres, whose contraction they can thus evoke in many regions of the ventricles. 7 In ungulates, Purkinje fibres are very large, pale and easily recognized: in man, the system is less obvious.
○ **Endocrine role of heart:** Atrial myocytes synthesize atrial natriuretic factor (ANF), which relaxes blood vessels and increases the excretion of sodium and water by the kidney. ANF is thus a partial counterweight to the renin-angiotensin system.	

LYMPHATIC VESSELS	
Lymphatic capillaries	**Collecting vessels**
1 Network of blindly ending or anastomosing tubes, 5-50 µm wide. 2 The wall is made of an endothelial tube, with a discontinuous basal lamina and fine anchoring fibrils. 3 The wall permits the capillary to collect water, solutes and macromolecules from the tissue spaces.	1 Lymph passes from capillaries into larger lymphatic vessels with very thin walls of endothelium, basal lamina and collagen, and numerous valves. 2 Lymph is led to small protective ovoid bodies - lymph nodes - through whose tissues it must filter before going further. 3 Lymph collects in the thoracic duct before entering the circulating blood at the left innominate vein; the right lymphatic duct also collects lymph for return to the bloodstream. 4 **Thoracic duct** (a) Intima of endothelium, BL, CT, some longitudinal smooth muscle and an elastic

4 Capillaries (i.e., a lymphatic drainage) are absent from the CNS, bone marrow, eye, and parts of the spleen.	lamina. (b) Thick media of mixed longitudinal and circular smooth muscle. (c) Thin adventitia of collagen and a little longitudinal smooth muscle, vasa vasorum and nerve fibres. (d) A valve is at the venous exit.

VARIETIES OF GLAND

1 Epithelial secretory layer→lining stomach and uterus. 2 Single cells amongst others in an epithelium -goblet cells, secreting glycoproteins, which with water, make mucus. Mucus is vital for the protection and lubrication of epithelial surfaces. 3 Intra-epithelial clusters of glandular cells→ in urethra.	○ Glands as structures distinct from an epithelium can hold more synthesizing cells, but remain related to the surface epithelium by a duct - exocrine type of gland. ○ Other glands originate in an epithelial layer, but lose their duct and send their secretion instead into blood capillaries - endocrine or ductless glands.
○ **Exocrine glands, which may be:** (a) Simple, with one duct have secretory units (end-pieces) of a form either: .. (i) tubular (straight, coiled, branched), or .. (ii) acinar/alveolar (dilated acini may be termed saccules). (b) Compound with a branching duct system and secretory units of three forms: .. (i) tubular, .. (ii) acinar/alveolar, .. (iii) mixed tubulo-alveolar.	○ Endocrine glands making hormones: details in Chapters 26 and 27. ○ Mixed exocrine and endocrine glands, e.g., pancreas. ○ Mixed germinal exocrine/cytogenic (forming reproductive cells) and endocrine - testis and ovary. ○ Neurosecretory nerve cells and their axons constituting a neurofibrous gland are an exception to glands' being epithelial. ○ This classification takes on more meaning when all glands in all the organs have been studied.

15- STRUCTURE OF A COMPOUND EXOCRINE GLAND

1 Encapsulated in fibrous CT which sends in partitions around lobes.
2 Septa (sheets of CT) divide the glandular tissue further into lobules. Septa carry ducts, blood and lymphatic vessels, and autonomic nerves and neurons.
3 Each lobule contains:

- Many epithelial, parenchymal cells grouped as tubules or alveoli, cut at a variety of angles to the plane of section.
- In each tubular or alveolar secretory unit, the cells lie on a BL and face inwards towards a very small lumen.
- The lumens lead to ducts, also seen in the lobule.
- Outside the BLs, in the spaces between alveoli are the blood capillaries, CT cells and autonomic nerve fibres of the supporting stroma.

- A duct system runs through and out of the lobule and the gland, converging and widening as :

Structure and site	Lined by
Intercellular canaliculi (alveolus)	Alveolar secretory cells
Alveolar lumen (alveolus)	Alveolar secretory cells
Intercalated duct (intralobular)	Squamous or cuboidal
Intralobular duct (intralobular)	Cuboidal epithelium
Interlobular duct (interlobular septum)	Columnar epithelium
Lobar duct (interlobar septum)	Pseudo-stratified columnar
Final duct (lamina propria of tract)	Stratified columnar

○ **Compound exocrine glands** were classified by their secretory product as serous (water+enzymes), mucous (glycoproteins), or mixed serous andmucous.

1 Serous acini have pyramidal darkly basophilic cells, with spheroid nuclei and apical zymogen (pro-enzyme) granules.
2 Mucous acini are made up of pale cells, with the nuclei flattened towards their bases, and a cytoplasm crowded with mucus/mucin droplets, which can be stained to reveal the presence of the sulphated or neuraminic-acid/sialic-acid moieties that confer viscosity on mucus.
3 Mixed acini/alveoli:
(a) Mucous cells, in the majority, surround the lumen.
(b) Serous cells lie at one end as a serous crescent/demilune between the mucous cells and the BL.
(c) Serous secretion may pass in fine intercellular canaliculi between the mucous cells to reach the lumen.

- Mixed glands may also form two products by having pure mucous and pure serous alveoli.

CYTOLOGY OF SECRETION

	Mucous acinus	Serous acinus
Size	Large	Small
Lumen	Wide	Narrow
The cells	Cuboidal	Pyramidal
The cell boundary	Well-defined	Ill-defined
The cytoplasm	• Pale basophilic due to presence of rER. • Vacuolated due to presence of mucous.	• Basalbasophilic due to presence of RER • Apicalacidophilic granules (zymogen granules).
The nucleus	Flat, basal.	Rounded, near center.

Liberation of secretion	Myoepithelial cells	Duct-lining cells

1. Merocrine/epicrine/eccrine manner involves exocytosis, or the discharge of only secretory material without any loss of cytoplasm, as in a serous gland. The cell then returns to the synthesizing phase of its secretory cycle. 2. Holocrine secretion requires that the cell fill itself up with secretion which is liberated by the cell's breaking open and dying, e.g., in a sebaceous gland. Precursor cells must multiply to replace those lost, for the gland to continue secreting. **3.** Apocrine way was thought to involve a significant loss of apical cytoplasm along with the secretion, milk fat, departs from the mammary cell enclosed in a membrane but not cell death.	**1.** These lie between glandular and duct cells and the BL, and clasp those cells in long branching processes filled with filaments. **2.** They closely resemble smooth muscle cells, and contract to help squeeze the secretion out of large exocrine glands (breast and salivary) or the long, tortuous sweat gland.	**1.** Ducts are not usually passive tubes for conveying secretions. Their lining cells often are cuboidal or columnar, and acidophilic, with many basal mitochondria serving active transport mechanisms to modify the secretion's concentration and electrolyte composition, by actions similar to those of kidney tubules. **2.** Such ducts may be called secretory or striated (from the many parallel mitochondria); they lead to less active excretory (drain pipe) ducts.

16- MICROSCOPIC TECHNIQUES FOR BLOOD

1 stained with a Romanowsky-type combined stain - a neutral combination of acidic (eosin) and basic (azure) stains.
2 In the stained smear, a differential count by eye or automated counter gives the proportions of the different varieties of leucocyte.
3 Absolute counts of blood, diluted by a known amount, in a counting chamber give the numbers of the formed elements
4 Phase-microscopy and videorecording of leucocytes alive in fresh blood on a warmed slide under a sealed coverslip.
5 Tagged monoclonal antibodies to recognise cell-surface glycoproteins characteristic for particular subtypes of blood cell. This approach allows a specific cell population to be sorted for culture and study using automated flow cytometry.

ERYTHROCYTES

1. Biconcave discs; close to 7.5 µm diameter in a smear. 2. Comprise a flexible membrane enclosing haemoglobin (iron-porphyrin-protein) in a closely packed state which, with membrane-spectrin-actin interactions, maintains the RBC's optimal shape for gas exchanges involving the haemoglobin. 3. Osmolarity of the plasma affects the shape of an RBC. Hypertonic solutions in vitro cause crenation and shrinkage; hypotonic, swelling and haemolysis. 4. Globin is acidophilic, and RBCs stain orange with eosin. 5. Mature RBCs have no nucleus, Golgi body, ER, ribosomes or mitochondria. 6. RBCs do have glycolytic enzymes and substrates, and methaemoglobin reductase and carbonic anhydrase for their respiratory function: (a) Oxygen binds to ferrous iron of haemoglobin (RBC) for transport: air --> lungs -- > blood --> tissues (b) Carbon dioxide leaves bicarbonate of the plasma and carbaminohaemoglobin (RBC) for transport: tissues --> blood --> lungs --> air	7. Reticulocyte/polychromatophil erythrocyte. An immature RBC, when stained supravitally with cresyl blue, has a blue condensed network of clumped, residual ribonucleoprotein not yet used for protein (globin) synthesis. 8. Life in circulation is estimated by ^{51}Cr labelling at around 120 days, then the RBC is sequestered in the spleen, liver or bone marrow to be phagocytosed by macrophages. The spleen is most responsible. 9. The volume of RBCs as a percentage of centrifuged whole blood - the haematocrit - is a quick, crude measure of the O^2-carrying quality.

LEUCOCYTES

- These are true cells, divided according to the granularity of their cytoplasm into two groups - granular and agranular.

Granular leucocytes

- All kinds appear round in a smear with a diameter 10-14 µm. - Polymorphonuclear neutrophil (neutrophil/PMN/polymorph). (a) Nucleus has coarse, clumped, deeply staining chromatin, usually in two or more lobes or segments connected by thin chromatin strands. Unlobated band nuclei are in immature cells; older nuclei have several lobes. (b) Cytoplasm is granular from many, small, weakly staining (neutrophil) granules of two kinds: .. (i) non-specific azurophil granules that are lysosomes with destructive enzymes; and .. (ii) numerous specific non-lysosomal granules holding a selectin-type glycoprotein for adhesion to endothelium and ECM, and lysozyme, and other bactericidal substances.	(c) This motile cell is attracted out of vessels into the tissues, where it attacks bacteria and phagocytoses them and immune complexes. The attack on bacteria is two-pronged: .. (i) with a respiratory burst that generates free radicals; also myeloperoxidase catalyzes the production of hypochlorous acid; and .. (ii) by proteins, e.g., defensins, and bactericidal permeability-inducing protein (BPI), that damage bacterial cell walls. (d) PMNs make up 55-65 per cent of the total leucocytes.

Eosinophil	Basophil
(a) Nucleus is darkly staining and bilobed. (b) Cytoplasm has many large, eosinophil granules 0.5-1 µm diameter, and some smaller core-less granules.	(a) Nucleus is bilobed and sometimes twisted, but palely staining and often obscured by

(c) Specific granules are a form of lysosome, which in EM have a crystalline core and a fine granular region. Defensive basic/cationic proteins, e.g., major basic protein, give the acidophil reaction. The enzymes differ somewhat from the neutrophil's, e.g., generating antimicrobial O_2 metabolites differently. (d) Motile, and enter inflamed tissues, especially at sites of allergies and parasitic infestations. They attack helminths using the basic proteins and oxygen derivatives, and also may dampen mast cell-dependent reactions, e.g., by phagocytosing mast-cell granules. (e) They comprise 2-3 per cent of leucocytes (but rising for (d)). (f) In EM, the large granules, like a skunk, have a dark lengthwise central stripe, which helps in identifying the eosinophil.	(b) basophilic cytoplasmic granules, containing sulphated proteoglycans, heparin and the vasodilator, histamine. (c) Basophils are reluctant to enter CTs, where there are mast cells holding the same materials. Thus, the function of basophils is in doubt, but they bind IgE and participate in various hypersensitivities. (d) They are rare; 0.5 per cent of the leucocytes.

Agranular leucocytes

Lymphocyte	Monocyte
(a) Small spheroid cell about 5-8 µm in diameter. (b) Large, spheroid, darkly staining nucleus leaves only a (c) Narrow rim of cytoplasm with a few small azurophil granules. (d) Motile to enter CT and epithelial tissue, but is not phagocytic. (e) Larger lymphocytes up to l2 µm diameter, with more abundant cytoplasm, may be seen in small numbers. The large granular lymphocyte is the natural killer cell. (f) Unlike granular leucocytes, small lymphocytes can be stimulated to enlarge and divide by antigens, cytokines, and some plant lectins. (h) Lymphocytes circulate in blood and lymph systems and migrate to CT and mucous membranes. Some lymphocytes have a lifespan of months or years. (i) They amount to 25-35 per cent of the leucocytes.	(a) Large, spheroid cell about 12-20 µm in diameter. (b) Nucleus has fine chromatin not densely stained, and is an indented sphere. (c) Golgi body and centrioles lie by the nuclear indentation. (d) Cytoplasm is abundant, with a few granules that are precursors of many larger lysosomes seen in EM when the cell is actively phagocytic. (e) Motile, to leave the vessels after only a day or so to become the phagocytic macrophages/histiocytes of CT, or other derivatives. (f) Macrophages/MØs spend months in CTs cooperating with lymphocytes in defensive responses (g) They comprise 3-l0 per cent of the leucocytes.

PLATELETS

1 Rounded or ovoid parts of cells, 2-5 µm diameter.
2 Consist of cytoplasm, organelles and inclusions, bounded by a cell membrane, reflecting their formation as pseudopodia breaking away from extravascular cells - megakaryocytes.
3 The dense central granulomere (organelle zone) has mitochondria, dense bodies and alpha granules; the pale peripheral hyalomere (sol/gel region) is cytoplasm deficient in organelles, except for contractile filaments and a shape-giving ring of microtubules.
4 Platelets adhere to collagen, neutrophils and monocytes, and especially to each other; this platelet aggregation/agglutination is used to seal defects in blood-vessel walls.

BONE MARROW

1 The naked-eye appearance of fresh, unstained marrow may be red from many developing RBCs, or yellow from mainly fat cells.
2 Red marrow has many elements:
(a) Blood sinusoids are lined by endothelial cells on an incomplete BL. Collagen fibrils (reticular fibres) support these, and
(b) adventitial stromal/reticular cells, similar to fibroblasts, but extending processes between, and greatly influencing, the haemopoietic cells.
(c) Macrophages cleanse blood, and detect and destroy worn-out RBCs and other elements. The iron recovered is stored, combined with protein as ferritin granules, before release to the labile pool and reuse.
(d) Blood cells develop extravascularly, are stored, then released through the sinusoidal wall into the circulation.
(e) Megakaryocytes form and release platelets.
(f) Fat cells are present, large and empty of fat in embedded sections.
(g) Bone surface cells act as an enclosing sac for the marrow.
3 Microscopic methods for marrow include sections, and smears of aspirated sternal marrow stained with a blood stain.

17- LYMPHOID ORGANS

- The primary lymphoid organs - thymus and fetal bone marrow - store, release and confer competence on the lymphocytes that populate the secondary organs and CTs, but do not participate directly in defence.

○ **Lymphocytes migrate in the blood and lymphatic flows for:** .. (a) the initial colonization of spleen, etc; .. (b) a constant vigilant patrol by recirculation around the body, as memory or	○ **The secondary lymphoid organs provide:** (a) APCs/reticular cells and macrophages to activate lymphocytes; (b) many lymphocytes to respond to a major antigenic challenge coming via the blood (spleen) or lymph (nodes); (c) lymphocytes to propagate the immune response further, say, to recruit other

naïve cells;
.. (c) the propagation of an active immune response, as activated cells.

nodes;
(d) a cleansing action by macrophages to remove undesirable materials from blood and lymph undesirable.

MUCOSO-LYMPHOID ORGANS

1 Aggregates of nodules occur in the tonsils, appendix and ileal Peyer's patches of the GI tract; whereas solitary nodules may exist anywhere in the mucosae of all tubular systems open to the outside.
2 Wherever nodules may be found, close by are lymphoid cells dispersed more diffusely.
3 The gut- and bronchus-associated diffuse lymphoid tissues (GALT, BALT) are notable. MALT (mucosa-associated lymphoid tissue) usually refers to the unorganized lymphoid tissue of the gut.

4 Having an epithelium between the microörganisms and the connective tissue, where most of the lymphoid cells reside, poses problems:
(i) Over the nodules, special low columnar epithelial cells - M cells - develop in order to pass antigens to the underlying antigen-presenting cells in the lamina propria. The APC and lymphocytes sometimes lie in a pocket in the M cell. ('M' for microfolds on the M cell surface.)
(ii) The antibodies subsequently made by the plasma cells are immunoglobulins of a kind that the typical epithelial cells can take up basally, and secrete apically into the lumen needing protection.
(iii) It is also necessary for certain types of lymphocyte to enter the epithelium.

LYMPH NODES

- Nodes are small bodies placed at intervals along the lymphatic vessels, and structured so that the lymph has to pass through them. Afferent lymphatics bring lymph from a drainage area.
- The node is responsible for combating intruders and confining infection to that area, by sending out antibodies and cells via efferent lymphatics.

- **Lymph-node structure**

1 A CT capsule, with some smooth muscle cells, sends in thin CT trabeculae, supporting a network of reticular fibres, and reticular cells of fibroblastic and the accessory dendritic kinds.
2 A denser outer cortex and a looser, inner medulla are present.
3 Efferent lymphatics leave at a hilus: the point of entry for blood vessels, serving a mostly cortical microvasculature.
4 Afferent lymphatics open through the capsule at several places to feed a system of 'sinus' channels running so: subcapsular/marginal sinus --> cortical/intermediate sinuses --> medullary sinuses --> efferent lymphatics.(Sinuses are lined by reticular cells, accompanied by macrophages)
5 Denser masses of lymphoid tissue, extensive and follicular/nodular in the cortex, and continuing into the medulla as widely spaced medullary cords, have packed cells: lymphocytes, lymphoblasts and antigen-trapping dendritic reticular cells with processes. Lymphoblasts/centroblasts occur in the paler germinal centres of the cortical follicles. The follicular zone contains B lymphocytes separated by follicular dendritic cells (FDCs).
6 The deeper lying paracortical region has mostly T lymphocytes, and dendritic APCs wrapping so intimately around lymphocytes that they received the name interdigitating reticular cells (IPCs).

- **Lymph-node functions**

1. Mechanical filtration of lymph (soot carbon particles)
2. Phagocytosis of materials in lymph by macrophages
3. APCs and MØs process antigens for lymphocyte activation.
4. Proliferation of sensitized lymphocytes to become lymphoblasts.
5. Recirculation of mature lymphocytes from venule blood to sinus lymph by migration through the cuboidal endothelium of the venules (high-endothelial venules - HEVs).

SPLEEN

- Lies in the upper left of the abdomen, but there may also be small accessory spleens. It receives blood from the splenic artery for a treatment similar to that given the lymph by the node.

- **Splenic structure**

1 Thick fibro-elastic CT capsule has some myofibroblasts and a covering mesothelium.
2 Internally, thick CT trabeculae bear branches of the splenic artery and veins, entering and leaving at the hilum.
3 To the naked eye, most of the freshly cut organ is red pulp with white spots - white pulp.
4 Red pulp consists of a loose reticular tissue infiltrated with blood cells, and arranged in the so-called cords of Billroth around sinusoidal channels/sinuses - a Swiss-cheese situation of red-pulp cheese and sinusoidal holes.
The outermost white pulp, abutting the red pulp, is a boundary zone - the marginal zone, not to be confused with the mantle zone of densely packed mature lymphocytes around germinal centres.
5 Cord tissue has dendritic and fibroblastic reticular cells, and collagen fibrils supporting macrophages, and white and red blood cells.
6 Sinusoids/sinuses are lined by non-phagocytic endothelial/littoral cells, separated by slits and oriented longitudinally on a fenestrated BL. Blood cells thus can pass from sinusoid to cord and back, and cordal macrophages can extend pseudopodia into the sinusoidal lumen.

- **Splenic blood flow**

1. Fed by the splenic artery, a trabecular artery branches out away from the CT as a central artery (arteriole) of the white-pulp lymphoid sheath, which it supplies by small branches. The artery is not central in the nodules.
2. The arteriolar branches of the central artery turn towards the red pulp, as several very straight branches - penicilli/pulp arterioles.
3. The vessels become smaller, and some have discontinuities in the BL, and gain a sheath of macrophages - sheathed capillaries – before the terminal capillaries open into a cord (Open Circulation Theory) or a sinusoid (Closed/Fast Circulation). Probably both kinds of termination exist.

7 White pulp is a dense lymphoid tissue ensheathing branches of the arteries, once these have left the trabeculae. The sheath (PALS) dilates into follicles/nodules, some with germinal centres. 8 Lymphocytes are predominantly B in the nodules, and T in the periarterial lymphoid sheath (PALS). To match, reticular antigen-presenting cells are follicular/dendritic in the B-zone, interdigitating (IDCs) in the T-zone.	4. Sinusoids and cords both contain blood. 5. Pulp venules collect the blood and carry it to trabecular veins for return to the hilum,and exit via the splenic vein.

- **Splenic functions**

1 Until birth, the spleen takes part in myelopoiesis, as do lymph nodes.
2 White pulp serves for:
.. (a) recirculation of lymphocytes;
.. (b) formation of new lymphocytes and plasma cells for immune responses to blood-borne antigens, met first at the marginal zone.
3 Red pulp provides:
.. (a) blood cleansing by the sequestration and phagocytic destruction by macrophages of unfit blood cells and platelets, and bacteria;
.. (b) metabolic breakdown of RBCs so that their iron can be reused;
.. (c) a place to accumulate platelets;
.. (d) sites by the marginal zone for plasma cells after antigenic stimulation, analogous to the cords and medulla of the active lymph node.

THYMUS

- **Situation and basic structure** 1 Lies in the upper midline of the thorax. 2 Markedly lobulated, with thin partitioning septa of fibrous CT, and adipose tissue which increases greatly with age. 3 In each lobule, a cortex surrounds a more palely staining medulla. 4 However, the medullary tissue is continuous from lobule to lobule as an axial cord.	- **Thymic finer structure** - Cells are: (a) packed lymphocytes (thymocytes), less densely packed in the medulla, making it paler, supported by (b) stellate epithelio-reticular cells of pharyngeal-pouch endodermal origin, not phagocytic, and with their processes attached by desmosomes (note that the main thymic stromal cell is thus anepithelial cell); (c) pale interdigitating dendritic/reticulum cells in the medulla; (d) a few macrophages in cortex and medulla; (e) some myoid cells, resembling dystrophic skeletal muscle fibres; 2 Absent are afferent lymphatics, germinal centres, and significant numbers of reticular fibres. 3 Epithelio-reticular cells form concentrically lamellated, rounded, keratinizing, eosinophilic bodies - thymic/Hassall's corpuscles - in the older medulla. 4 Blood capillaries have intact basal laminae, few fenestrations in the endothelium, and an outside sheath of epithelio-reticular cells: all comprising the basis for a barrier hindering cells, e.g., B cells, and perhaps blood-borne antigens, from reaching the thymic cortical lymphocytes.

18- SKIN

Skin/integument covers the body and serves many functions. It consists of a thick, protective, cornified, stratified squamous epithelium (epidermis), on a firm, dense CT lamina propria (dermis), and has special appendages, hair and nails, and accessory glands, sweat, sebaceous, and mammary glands (

LAYERS OF EPIDERMIS

1 Stratum corneum of keratinized cells (outermost). 2 Stratum lucidum, a thin pale layer of keratin seen when the stratum corneum is very thick. 3 Stratum granulosum of cells with basophilic granules. 4 Stratum spinosum of keratinocytes/prickle epithelial cells. 5 Stratum germinativum, bordering on the BL.	**Stratum germinativum/basale** (a) Keratinocyte precursor cells, cuboidal or columnar in form, lie on a BL. (b) Cells project down many small basal processes. (c) The whole underside of the epithelium is indented by CT dermal papillae for effective attachment, nutrition, and sensation. (d) Cells proliferate to replace lost surface cells.

Stratum spinosum

(a) Keratinocytes/prickle cells ... (i) Principal cell kind; ectodermal in origin; move upwards in the layer and continue to proliferate, despite the many desmosomes holding them together (which, with processing shrinkage, lead to the cells' spiny, prickly appearance). ... (ii) Cytoplasm is rich in keratin filaments, bundled into tonofilaments and increasing	**(b) Melanocytes** ... (i) Ectodermal; but migrated neural crest cells. ... (ii) Constitute 1 in 4 to 1 in 10 of basal epithelial cells. ... (iii) Deficient in tonofilaments and desmosomes. ... (iv) Synthesize melanin and transfer it via their long dendritic **processes** to neighbouring keratinocytes. ... (v) UV light causes greater melanin formation and a thickening of the keratin layer. Pituitary and adrenal hormones also increase pigmentation, which is a useful sign for diagnosis. **(c) Langerhans cells** are poorly phagocytic, marrow-derived, specialized macrophages, with long dendrites. They are antigen-presenting cells, accessory to T-cell immunity. **(d) Merkel cells** are sensory cells with vesicles and a polylobulated nucleus. They attach to

in number towards the keratin layer, and formed from prekeratin monomers.	disc-shaped endings of some of the axons that penetrate the epithelium.

Strata granulosum and corneum

(a) Stratum granulosum cells form a kerato-hyaline matrix from their basophil granules, binding together packed tonofilaments within the cells to convert the cells to soft keratin. Other organelles and the nucleus vanish, while the plasmalemma thickens and toughens, to build a cornified envelope. (b) Flattened, dead, keratinized, surface cells desquamate. (c) Only with EM is keratin seen to be cellular. In the usual HE preparation it is eosinophilic, and often splits and breaks.	(d) Epidermis is thrown up into ridges - cristae cutis - on the palmar and plantar surfaces of the hands and feet: the basis of finger and palm prints. (e) At the top of the ridges, spiralling holes open through the keratin to let out the sweat. (f) Keratin layer may be very thick, for instance on the soles and palms. Such thick skin is hairless, and lacks sebaceous glands.

DERMIS (Corium)

1 Divided into layers: papillary, fine-textured CT adjacent to the epidermis, and a deeper reticular layer. 2 Reticular layer is thick collagenous CT of a variable thickness, not always related to that of the overlying epidermis. 3 Elastic fibres of the dermis give skin its elasticity, but cause wounds to gape. Ruptured dermis often heals as a white line visible through the epidermis, e.g., a mother's stretch marks. 4 Has the usual cells of CT - fibroblasts, macrophages and other defensive cells, and sometimes pigment-bearing chromatophores/dermal melanocytes. 5 Smooth muscle of arrectores pilorum, nipples and scrotal dartos, and skeletal muscle in the scalp and face, are attached in the dermis.	6 Blood vessels are derived from arterial plexuses: a deep cutaneous plexus/rete, and a subpapillary plexus sending capillary loops up into dermal papillae. Lymphatics accompany blood vessels. Blood flow is varied greatly by shunts through glomi (coiled arteriovenous anastomoses), and by the constriction or relaxation of arterioles. 7 Nervous receptors (Chapter 12.B), with sensory nerve fibres are present; and autonomic nerve fibres: .. vasomotor to vascular smooth muscle, .. pilomotor to hair arrector muscles, .. sudomotor to sweat glands. 8 Hair follicles and glands lie mostly in the dermis.

SWEAT GLANDS (Glandulae sudoriparae)	SEBACEOUS GLANDS
1 Single coiled tubules, lined by simple cuboidal light and dark cells; distributed over the body except for the lips, glans penis and inner prepuce. 2 Secretory part lies in the lower dermis, or subcutaneously in the hypodermis/superficial fascia. One tubule is cut through many times in one section. 3 The secretion, mainly water and electrolytes plus some lipids, is led to the epidermis through a duct, lined by stratified cuboidal epithelium, then through the living/Malpighian layer and a spiralling hole in the keratin. The gland's chloride channel is one that is impaired in cystic fibrosis. 4 Myoepithelial cells are seen within the basal lamina of the secretory tubule. Their contraction is under autonomic control. 5 The larger variety of gland seen in the axillary, perianal and perigenitalial regions is termed apocrine, in contrast to the eccrine glands in the majority. Apocrine glands become active with pubertal development of the ambosexual hair, and may be related to animals' scent glands. 6 The ceruminous glands of the external auditory meatus seem to be enlarged sweat glands, producing a secretion of pigmented lipids.	1 Pear-shaped, simple, branched alveolar, with large cells, usually looking vacuolated because their fatty content is dissolved out. 2 Several glands are clustered by the side of a hair follicle, into which they discharge the secretion - sebum. Their short duct is lined by stratified squamous epithelium. 3 Sebum, formed in a holocrine manner by the total breakdown of the cells, may lubricate the hair shaft, protect the skin from drying and moisture, and be bacteriostatic. 4 Lie independently of hairs on the labia minora, glans penis, in the oral mucosa by the red margin of the lips, and as the Meibomian glands of the eyelid. They are absent from the palms and soles.

HAIR

Varieties and sites

1 Lanugo - fine, fetal, hairy covering, shed at birth. 2 Replaced by the vellus - fine body hairs. 3 Scalp, eyebrow and eyelash hairs are thicker.	4 Ambosexual hair - pubic and axillary. 5 Masculine hair - face (beard), chest and extremities.

Hair development

1 Hair is a hard keratin derivative of the epithelium of a hair follicle. 2 In development, an epithelial bud grows down from the young epidermis; a vascular CT dermal papilla invaginates the bud; in the bud a germinal matrix develops, forming the special keratin; and side buds form sebaceous glands. **3 Hair shaft comprises:** (a) Medulla, as the central core of soft keratin and sometimes air spaces. The medulla may be absent. (b) Cortex of closely packed, elongated, hard-	**4. Hair follicle** (a) Outer CT sheath and inner basal lamina (hyaline membrane). (b) Vascular papilla lies directly under the synthesizing epithelial area, responsible for the upward growth of the hair and its inner root sheath. (c) External root sheath is a continuation of the epidermal living layer, expanding to form the basal hair bulb. (d) Internal root sheath forms a cuticle layer from which the other cuticle, on the hair, can separate at the level of entry of the sebaceous gland's duct. The internal root sheath thus comprises: (a) innermost cuticle cells, (b) Huxley's layer of cells with trichohyaline granules, (c) Henle's single, outer layer of clear cells.

keratinized cells, formed without any intermediary kerato-hyaline granules developing. Melanin and other pigments may be incorporated in the cells during keratinization. (c) Cuticle - outermost coat of shingled/imbricated cells, with their free edges projecting upwards.	(e) Epidermal germinal matrix, above the papilla, forms the hair's cuticle, cortex and medulla. NB - the appearance of cross-sections varies with the level in the hair follicle at which they are taken. (f) Arrector pili of smooth muscle fastens the lower hair bulb's CT sheath to the upper dermis nearby.

- **Epithelial replacement and hair growth** are cyclical, not constant activities. The hair stops growing, via a relatively short catagen period of regression or involution, to enter a long non-growing telogen phase of being a club hair, which eventually falls out. It is replaced during an anagen/growth phase by a new hair from the reactivated deep region of the follicle.
- **Pilomotor activity**: Hairs are raised from their relaxed, inclined attitude by contraction of their arrectores pilorum muscles in response to cold, so that more insulating air is trapped near to the skin. Hairs also 'stand up' in fear and other emotional reactions.

NAIL	SKIN FUNCTIONS
1 The horny plate of hard beta keratin is synthesized by 2 the proximal, germinal, part of the nail bed. 3 The nail bed comprises the living layers of the epidermis, ridged longitudinally, and lacking glands and follicles. Part of its germinal region is seen by the naked eye as the 4 lunule, the pale half-moon area just distal to the eponychium - an extension of the stratum corneum of the dorsal skin.	1 Protection against water, bacteria, sunlight, mechanical forces, dehydration, cold, etc. 2 Retaining body fluids, i.e., protection against dehydration. 3 Temperature regulation by: (a) varying peripheral blood flow, (b) sweating, (c) hair elevation, and (d) insulation by adipose tissue under the skin. (Note that heavy sweating defeats 2 above.) 4 Food storage and fat metabolism in the subcutaneous hypodermis. 5 Vitamin D formation by the action of ultraviolet light. 6 Sensory appreciation of the environment by nervous receptors: Chapter 12.B.L. 7 Friction surface for motor tasks involving grasping, rubbing, scratching, etc. 8 Display and communication: social, sexual, and diagnostic. Many diseases distinctively affect the skin and its hair and nails.

19- RESPIRATORY TRACT TO LUNGS

Nasal cavity

1 Divided by a hyaline-cartilage nasal septum in the midline. 2 Stratified squamous epithelium (hairy) of the nares changes to 3 a lining nasal mucosa of: .. (a) pseudostratified, columnar, ciliated epithelium with mucus-secreting goblet cells, on .. (b) a loose lamina propria, with many leucocytes, blood vessels, and mixed muco-serous glands. 4 Venous plexuses, to warm the air, underlie the epithelium. 5 Turbinate bones in the conchae support the mucosa. 6 A small part of the mucosa is olfactory, with a neuroepithelium and Bowman's glands. 7 Paranasal air sinuses open off the main cavity. 8 The folded pharyngeal tonsil, covered by pseudostratified, columnar, ciliated epithelium, lies posteriorly in the pharynx.	**9 Nasal functions:** (a) air-filtering, material trapped in mucus is swept by the cilia towards the pharynx, (b) air-warming, (c) air-humidifying, (d) olfaction, (e) sensitivity for nasal reflexes such as sneezing, (f) resonating the voice.

Larynx	Trachea
1 Hollow chamber, whose walls are supported by cartilages, connected by ligaments and membranes, and moved by skeletal muscles. 2 The extrinsic and intrinsic muscles move the larynx up and under the epiglottis in swallowing, and move the cartilages and tense the vocal cords during phonation and breathing. 3 The cartilages are hyaline tending to calcification, or elastic for the epiglottis, cuneiforms, corniculates, and the apices and vocal processes of the arytenoids. 4 Mucosa is mostly pseudostratified, columnar, ciliated epithelium with goblet cells, on a loose lamina propria rich in elastic fibres, mucous and mixed glands, leucocytes and sometimes lymphoid nodules. 5 Two constrictions occur: the false vocal cords/ventricular folds; and the lower, true, cords. The true vocal chords are elastic ligaments tensed by the adjacent vocalis muscle, and are covered with stratified squamous epithelium. There are no glands in their lamina propria. 6 The epiglottis, too, has stratified squamous epithelium on its exposed tip and upper surface.	1 Flexible, extensible tube, with an always-patent lumen. 2 Mucosa as for the larynx, and the cilia sweep towards the pharynx, but the elastic fibres run longitudinally as a layer between mucosa and submucosa. 3 Supporting C-shaped pieces of hyaline cartilage are incomplete on their oesophageal side. 4 The gap in the C is crossed by trachealis smooth muscle and CT. 5 Outer adventitia is fibro-elastic CT.

LUNGS

- The structure of the lungs reflects the way in which the air is moved:

(a) the lungs are covered by a slippery membrane and are enclosed in another membrane, adherent to the inner chest wall, with a potential space between;
(b) the lungs are stretched out against their considerable elasticity, so that this space remains only a potential one;

(c) the larger conducting tubes of the lung need firm cartilages in their walls to prevent their collapsing during the inspiratory sucking in of air.

Bronchial tree serving the lungs	Mucosa of the lower airway
1 Primary bronchi branch to form the 2 intrapulmonary lobar bronchi, branching to form segmental bronchi, then lobular bronchioles. After about 9-l2 generations of branching, bronchioles replace bronchi. 3 Terminal bronchioles lead to respiratory bronchioles, off which open the respiratory exchange units, and not just at the end, but along the bronchiole. 4 Bronchi resemble the trachea in structure, except that the cartilage pieces in the wall have very irregular shapes, and the smooth muscle forms a nearly complete layer - muscularis mucosae - between the cartilages and the lumen. 5 Bronchioles are smaller than bronchi: .. they have no cartilages; .. their elastic fibres merge with those of the surrounding lung tissue; .. the epithelium changes to simple, low ciliated columnar with a few goblet cells; .. no mucous glands are present in the lamina propria, where the smooth muscle is relatively substantial. 6 Sharing the connective tissue of the branching bronchi are blood vessels, nerves and lymphatic vessels, entering or leaving at the hilum or lung root. 7 Hilar structures include arteries (bronchial and pulmonary), veins, lymphatics (from two systems), bronchi, lymph nodes, ganglia, nerves (to bronchial, bronchiolar, and vascular smooth muscles; and sensory), and adipose and other CT.	1. Cell types in the epithelium: (a) ciliated columnar cells, with lysosomes and some microvilli; (b) mucus-secreting goblet cells; (c) basal 'undifferentiated' cells to replace the specialized kinds; (d) Clara's non-ciliated bronchiolar secretory cells with granules and GER; (e) neuroendocrine cells; (f) lymphocytes migrated from the lamina propria. 2. A sheet of sticky mucus is moved by ciliary action over the mucosa to catch and remove particles - the mucociliary escalator. 3. The basal lamina typically is thick. 4. Muco-serous mixed glands, where present in the lamina propria, are small, compound tubular, and respond under nervous control to irritant stimuli, e.g., smoke.

Respiratory chambers	Interalveolar wall
1 Respiratory bronchiole has simple, low columnar or cuboidal bronchiolar and ciliated cells; elastic fibres and smooth muscle support the epithelium's BL. 2 Opening out along the respiratory bronchiole are alveoli, whose openings are ringed by smooth muscle. 3 At the end of the respiratory bronchiole are one or more long alveolar ducts. 4 Alveolar ducts can be viewed as being three to six atria, vestibules, leading to alveolar sacs, made up of varying numbers of alveoli. Processing distortions in lung slides often make the atria and sacs hard to make out. 5 One alveolus or cubicle shares an alveolar wall with the ones adjacent and backing on to it. The wall is thus interalveolar and carries the many capillaries, whose blood is to receive oxygen and give up carbon dioxide. 6 Angiotensin converting enzyme in pulmonary capillaries cleaves angiotensin I to make it the potent angiotensin II.	1 Air side - continuous alveolar epithelium with: .. (a) type I pneumocytes/squamous cells; and .. (b) pneumocytes type II/septal or great alveolar cells, with prominent lipid cytosomes/ multilamellar bodies in their cytoplasm. 2 Surfactant is a stabilizing fluid film of lipids (90%) and proteins (10%), covering the epithelium and lowering surface tension. The type II cells synthesize this film, but also are the stem cell to replace themselves and Type I cells. 3 Alveolar macrophages/dust cells lie free in the alveoli. 4 Alveolar epithelium lies on a basal lamina sometimes merging with, and sometimes separated from, the 5 basal lamina of a blood capillary, on which lies an 6 unfenestrated endothelium on the blood side. 7 Where the two basal laminae are separated, the space - zona diffusa - is taken by elastic and reticular fibres, fibroblasts, macrophages and other CT cells. 8 The pulmonary blood-air barrier can therefore be as thin as 300 nm, and has a very extensive area. 9 Communication between adjacent alveolar sacs is through holes in the wall - alveolar pores. l0 Basal laminae, fibres, and surfactant maintain the shape and patency of alveoli during respiration.

- **Pleurae** are fibro-elastic vascular membranes with mesothelial coverings. From the visceral pleura, CT septa run in to subdivide the lung into lobules and carry lymphatic and venous vessels.

20- KIDNEY

- This separates from the blood large quantities of ultra-filtered fluid in more than a million small, tubular units, nephrons/uriniferous tubules. Most needed materials are then recovered to the bloodstream, and some secretion of other substances occurs, to give a solution of unwanted materials -the excretion - to be collected as urine from the tubules.
- The kidney is a compound, tubular, excretory gland, and an endocrine gland.

Kidney's general architecture

1 Outside are perirenal fat, and nearby suprarenal glands. 2 Thin, fibrous capsule. 3 Reniform (kidney-shaped!), around	9 The human kidney is multilobar, with 8-l8 lobes. l0 Pyramidal tissue has a pale striated appearance from many parallel tubules and blood vessels. It is the medulla. ll The outer cortex of the kidney is darker, with many round structures -

a hilum and sinus for the 4 renal artery, renal vein, and ureter. 5 Ureter opens from a renal pelvis, for which 6 major and minor calyces* collect the urine from 7 bluntly pointed apical papillae of pyramids. 8 Pyramid + overlying tissue constitute a lobe.	renal corpuscles/Malpighian corpuscles, and coiled tubules cut in cross and oblique section. l2 Cortical tissue - columns of Bertin - runs inward to partly separate the pyramids. l3 Medullary tissue extends rays up from the medulla into the cortex. A medullary ray defines the centre of a lobule, but the lateral limits of the lobule remain undefined in the cortical tissue.

Form of nephron and relations with cortex and medulla

Cortex	Cortex
1 Renal corpuscle (round, l50-240 µm diameter) - glomerulus of epithelium-invested capillaries, and enclosed in a Bowman's capsule, opening out at the urinary pole into the 2 proximal convoluted tubule, which leads to the	5 Distal convoluted tubule follows, attached at one point to the renal corpuscle of origin; thence leading to an 6 arched collecting/junctional tubule joining a

Medulla	Medulla
3 descending limb of the hairpin loop of Henle, 4 then the ascending limb of Henle's loop.	7 straight collecting tubule, receiving many branches and running down from a medullary ray through the medulla to → 8 papillary duct of Bellini, opening at the papilla of the pyramid. The papilla is cribriform from the many openings.

Nephron cytology

Glomerulus	Proximal tubule (40-50 µm diameter)
(a) Blood is fed, via an afferent arteriole, under pressure into groups of capillaries, tufting out as loops from the vascular pole, and ensheathed in visceral squamous epithelium. (b) Glomerular wall of ... (i) fenestrated endothelium, ... (ii) thick basal lamina (two laminae fused together), ... (iii) podocytes' pedicels (visceral epithelial cells' feet), separated by filtration slits of controllable width, permit (c) the filtration of water and solutes, with a molecular mass less than 30 kDa, into a capsular space between (d) glomerular/visceral epithelium and the parietal squamous epithelium and BL of Bowman's capsule. (e) The altered blood is collected from the capillary tufts, and passes out via the narrower efferent arteriole. (f) Between the capillaries at their base lie mesangial cells, synthesizing and maintaining the glomerular basal lamina, and also probably phagocytic and contractile.	(a) Most common of those tubules seen in the sectioned cortex, since it is longer than the distal tubule. (b) Simple, acidophilic, cuboidal, epithelial lining cells with: large round nuclei; (c) very many microvilli (brush border), and a surface glycoprotein coat containing peptidases to reduce polypeptides; (d) vesicles and lysosomes just below the microvilli, and involved in endocytotic protein uptake and breakdown to amino acids; (e) marked lateral membrane infoldings and interdigitation with adjacent cells, (f) to which they attach with junctional complexes. (g) The basal region has many membrane infoldings and long mitochondria (basal striation) for the provision of energy for active transport of Na^+, and with it glucose and amino acids, through the basolateral membrane, (h) basal lamina, and thence into adjacent capillaries, with their fenestrated endothelium.

Thin segment (l5 µm diameter)	Distal tubule (20-50 µm diameter)
(a) Squamous epithelial lining on a BL. (b) Cells are pale, tightly fastened, with small, short microvilli, and a few mitochondria scattered randomly. (c) The lack of red blood corpuscles in the lumen, and plumper nuclei, distinguish thin segments from capillaries.	(a) Weakly acidophilic, cuboidal epithelial cells enclose large lumens. (b) No brush border is seen because only a few short microvilli are present. (c) Basal infoldings and interdigitations, with very many long mitochondria, give a basal striation. (d) Cells lie on a BL, also supporting fenestrated endothelial cells of the surrounding capillaries. (e) Macula densa is a specialized, more nucleated region of the epithelium, where it attaches to the arterioles of the glomerulus to form part of the juxtaglomerular apparatus. It senses the [Cl^-] locally in the distal tubule and signals, via mesangial cells, for renin release, and arteriolar and mesangial contraction.

Juxtaglomerular apparatus	Collecting duct (40-200 µm diameter)
(a) Afferent arteriole, nearing the JGA, loses its elastica interna. (b) Smooth muscle cells change to epithelioid with (c) secretory granules and some GER. (d) The juxtaglomerular secretory cells are in contact with the endothelium of the arteriole and, indirectly, with the macula densa of the distal tubule: for sensing (i) renal tubular chemistry, and (ii) stretch, indicating blood pressure. The cells' sympathetic innervation is another element in the control matrix.	(a) Pale cuboidal cells, with the lateral cell membranes prominent because lateral interdigitation is lacking, are of three kinds: (b) principal collecting-duct cells, and, set between them, alpha/A and beta/B intercalated cells, all differing in their ion-transport roles. (c) Principal cells have few microvilli, and few mitochondria, but are tightly connected by occluding junctions. Aquaporin 2 constructs the channels making the luminal cell membrane permeable to water in the presence of vasopressin/ADH, so that the cells reabsorb water. Basolaterally, a membrane Na,K-ATPase lets the cells secrete potassium, while absorbing sodium. (d) Intercalated cells have darker cytoplasm, and more and darker

(e) Granules are the enzyme renin for release into the blood, where it cleaves a potentially hypertensive polypeptide (angiotensin I) from angiotensinogen. (f) A juxtaglomerular interaction with the adrenal cortex and Na^+ excretion also occurs. (g) Polkissen/Goormatigh/lacis cells lie in the angle between the afferent and efferent vessels and the attached distal tubule.	mitochondria, than principal cells. The number of vesicles is highly variable, because they function to insert or remove ion pumps into the cell membrane, in a similar way to the gastric parietal cell. (e) Type A intercalated cells bear a luminal-membrane H,K-ATPase to secrete hydrogen ions and reabsorb potassium; type B cells have a luminal Cl/HCO_3^- countertransporter to secrete bicarbonate and recover chloride. (f) A simple columnar epithelium lines the final papillary ducts of Bellini, and covers the papillae.

Renal interstitium

1 lies between the kidney tubules and vessels.
2 It comprises: (a) reticular fibres, (b) a little ground substance, and (c) interstitial fibroblasts, looking after the matrix and secreting erythropoietin.
3 The interstitial elements are more prominent in the medulla than the cortex.

Renal blood vessels

1 Renal artery branches to form
2 interlobar arteries (interpyramidal), extending to the cortico-medullary junction, where they branch and turn as arching
3 arcuate arteries, giving off outward branches called
4 interlobular arteries; from which
5 intralobular arteries provide
6 afferent arterioles to
7 glomeruli; from the capillaries of which the blood is taken via
8 efferent arterioles to serve one or both of
9 two capillary beds - around the convoluted tubules, and between the straight medullary tubules.
l0 The blood collected in stellate, deep cortical, and interlobular veins, traces back the arterial path to the renal vein.
ll The sympathetic nervous supply to the kidney goes mainly to the renal vasculature, including the juxtaglomerular cells.
l2 Vasa recta is a collective name for arteriolar, capillary, and venous straight blood vessels in the medulla. They participate in the counter-current exchange.

URINARY PASSAGES

- The kidney's calyces and pelvis, and the passages to the urethra are lined by transitional epithelium.

Transitional epithelium/urothelium	Ureter
1 Multilayered, with large surface/umbrella cells, intermediate cells and basal cuboidal cells on a thin BL. 2 The surface cells have unique properties of: .. (a) making a barrier impermeable to urine; .. (b) changing their shape and extent during bladder distension. 3 the luminal umbrella cell membrane is asymmetrically thickened and has unusual lipids and proteins, including uroplakins 4 During bladder dilation, the vesicles attach to the thick luminal membrane and become part of it, thus increasing its extent and allowing the cell to flatten. No cell-over-cell sliding occurs, the cells being joined by tight and adhaerens junctions and desmosomes. 5 Large lysosomes destroy defective membrane. 6 The rate of cell turnover is very low for an epithelium.	1 Transitional epithelium lies on a collagenous lamina propria. 2 Mucosa has several longitudinal folds, giving the lumen a stellate shape in the cross-section. 3 Two smooth muscle coats: outer, circular; inner, longitudinal; (the terminal ureter has an extra, outer longitudinal one). 4 CT adventitia, rich in vessels and nerves.

Urinary bladder	Urethra (male)
1 Transitional epithelium, on a wide collagenous lamina propria without glands, constitutes the mucosa. 2 Three smooth muscle tunics interweave in the muscularis, in a pattern to squeeze the bladder empty. Retention of urine invites infection. 3 A CT adventitia has blood and lymphatic vessels, nerve fibres and ganglion cells. The part of the bladder facing the pelvic cavity has a serosa. 4 The ureters enter obliquely, with mucosal flaps to prevent reflux; smooth muscle forms a sphincter at the urethral outlet.	1 Epithelium lies on a very loose, elastic, vascular, distensible lamina propria. The lumen is stellate in cross-section. 2 Epithelium is transitional changing to pseudostratified columnar, stratified columnar, and finally stratified squamous, as it traverses the three sections: prostatic, membranous (short) and penile/cavernous (long). 3 Branching out in the penile mucosa are Littré's small tubular mucous glands. 4 There is a meagre smooth muscle muscularis, except at 5 the smooth and skeletal muscle sphincters 6 Female urethra is much shorter than the male; structurally it is similar, but, ending in the pelvic floor, has a skeletal muscle sphincter at its terminus.

21- ALIMENTARY SYSTEM

- Long, muscular, tubular structure for ingesting food and water, separating them from the intake of air, breaking the food down mechanically and chemically (digestion) for absorption, while propelling it anally.
- Ancillary glands, liver and pancreas are included, since they produce materials used for digestion or to be excreted via the tube, and they participate metabolically and in the control systems.

ORAL STRUCTURES

Salivary glands

1 Generally compound tubulo-alveolar, with intralobular intercalated ducts and secretory ducts (with basal striations), leading to interlobular excretory ducts.
2 Parenchyma is divided by CT septa into lobes and lobules.
3 Saliva is water, salts, and organic materials (mainly mucin and salivary amylase/ptyalin and maltase), with suspended lymphocytes (salivary corpuscles), epithelial cells, and bacteria.
4 Mucin is formed by mucous cells (pale in HE staining).
5 Enzymes are formed by serous cells (basophil, with zymogen granules).
6 Parotid gland is serous; submandibular/submaxillary has serous alveoli, and mixed tubules with serous demilunes/crescents; and the sublingual gland has mucous and mixed branched tubules, but lacks intercalated and secretory ducts.(The tubules are long enough to reach the excretory ducts.)
7 Smaller mucous and mixed glands are in lingual, labial, buccal, pharyngeal and palatine sites.

Lip

1 Core of fibro-elastic CT and skeletal muscle.
2 Outside is thin skin with hairs and glands.
3 Transition zone is the red margin/vermilion border, where the skin's cornified layer thins out; a rich capillary plexus is responsible for the colour. Glands are absent.
4 Inside is a thick stratified squamous epithelium, with mucous glands in its lamina propria.
5 The cheek is similar, but has more adipose tissue, and no red margin.

Gingiva/gum and raphe of hard palate

Stratified squamous epithelium (partly keratinized) on a dense CT lamina propria, with deeply penetrating papillae, and fastened tightly to tooth or bone.

Soft palate

1 Fibrous and skeletal muscle core, with mucous glands;
2 pseudostratified, columnar, ciliated epithelium covers the pharyngeal side, and stratified squamous the oral surface.
3 Functions in deglutition (swallowing), speech, blowing, coughing, and sneezing.

Tongue

1 Core is interlaced skeletal muscle bundles oriented in three directions, with attendant nerves and blood vessels.
2 Covered by stratified squamous epithelium, modified over the anterior dorsum by being thrown up with the dense lamina propria into projections called
3 papillae of various kinds, with special distributions:
(a) Filiform - most numerous, spiky, with a partly keratinized tip which is shed.
(b) Fungiform - less numerous, larger, with some taste buds in their smooth tops.
(c) Circumvallate - least numerous, largest, lie along the terminal sulcus, each surrounded by a trench, and with taste buds in its wall.
(d) (Foliate - small ridges on the sides of the tongue, prominent in rabbit, vestigial in man; also with taste buds in the walls.)
4 Lingual glands - (a) posterior mucous; (b) posterior serous of von Ebner, opening into the trenches; (c) anterior mixed sero-mucous.
5 Lingual tonsils are stratified squamous epithelium-covered aggregations of lymphoid nodules, with shallow crypts flushed out by mucous secretions of the posterior lingual glands.

Palatine/faucal tonsils

1 Covering is stratified squamous epithelium.
2 Deep, branching, epithelium-lined pits or crypts run down from the surface into the tonsils, but the epithelium is infiltrated by
3 lymphocytes produced in germinal centres of lymphoid nodules (often confluent) in the lamina propria, and by macrophages.
4 Immunoglobulins and lysozyme are present.
5 Glands and skeletal muscle lie nearby, outside the underlying CT capsule.
6 The palatine tonsils have substantial depth; the lingual are a narrow region interposed between the epithelium and the muscular core of the tongue.

Tooth

1 Anatomical features: crown, cervix/neck, root, apical foramen, pulp cavity, bony alveolus/socket, attaching periodontal ligament and the gingiva.
2 **Tooth components**
(a) Enamel: covers the crown of the tooth; tall tightly packed prisms/rods; 96 per cent mineral crystals, 4 per cent organic content; but completely acellular.
(b) Dentine: supports enamel and acts as the skeleton of the tooth; hard material of collagen fibrils, impregnated with crystals of calcium salts; penetrated from the pulp side by dentinal tubules enclosing long, thin processes of odontoblasts, whose bodies lie outside the dentine at the pulp.
(c) Cementum: a thin layer of bone-like material, with cementocytes (like osteocytes), but no Haversian systems, covers the root. Sharpey's collagen fibres of the periodontal ligament insert into cementum, and also into the bone of the alveolus, thus attaching the tooth to the jaw.
(d) Pulp: jelly-like ground substance, with CT cells, blood and lymphatic vessels and nerves, on a network of fine collagenous fibres; dentine's pulp-surface is covered with the columnar odontoblasts.

Histological details of tooth

(a) Decalcification for sectioning destroys mature enamel. It can be studied in the ground section.
(b) Enamel prisms have a spiral curvature to better withstand masticatory forces.
(c) Bands/striae of Retzius are growth/incremental lines across the enamel; Owen's contour lines are analogous features in dentine.
(d) Interglobular areas are poorly mineralized regions in the dentine.
(e) Dentinal tubules branch, and may penetrate a little way into the enamel as enamel spindles.
(f) Von Korff's 'fibres' seen in the pulp by young odontoblasts are either collagen awaiting incorporation into the matrix of the dentine, or are an artefact of silver impregnation.
(g) Secondary dentine (sometimes reparative) may be formed later to increase the thickness of the dentine.
(h) Epithelial attachment is a cuff-like extension of the gingival epithelium, attached to the neck of the tooth by glycoprotein.
(i) Acellular cementum lacks cementocytes.

Tooth development

4 (a) Two stages with (i) 20 deciduous/milk teeth, (ii) followed by 20 successional teeth and l2 permanent or accessional molars, totalling
(b) Involves complex inductive processes:
(i) Migrating neural crest cells become 'mesectoderm,'
(ii) and induce overlying ectoderm to thicken and grow down producing a
(iii) dental lamina, under which 'mesectoderm' cells group,
(iv) These induce the ectodermal dental lamina above to separate into tooth germs, and to provide for each an enamel/dental organ, with its stellate reticulum and inner and outer epithelia. The inner epithelium of the enamel organ, in its turn, induces
(v) 'mesectodermal' cells of the dental papilla to become odontoblasts, which form dentine.
(vi) The dentine acts as a stimulus to inner epithelium to become functional ameloblasts and deposit enamel on the dentine. Ameloblasts and odontoblasts are tall, columnar, secretory cells.
(vii) The enamel organ's epithelium extends down as Hertwig's root sheath, determining the form, size, and number of the roots.
(viii) The root sheath perforates, and, through the holes, cells of the surrounding mesectodermal dental sac approach root dentine and lay down cementum. Other sac cells become fibroblasts forming the periodontal ligament.

GASTROINTESTINAL TRACT

1 Mucosa (innermost)

(a) Of epithelium, lamina propria and smooth muscle muscularis mucosae.
(b) The epithelium in most places takes a glandular form, with simple tubular glands and a secreting surface epithelium.
(c) Some parts have discrete compound glands lying in the mucosa.
(d) Single lymphoid nodules can occur anywhere.

2 GI submucosa

(a) Of fairly dense CT, with blood and lymphatic vessels, and having a plexus of unmyelinated autonomic nerve fibres - Meissner's submucosal plexus.
(b) Glands are present in a few places.

3 GI muscularis externa

(a) Two or more helical layers of smooth muscle: the inner, tight 'circular'; the outer, loosely coiled 'longitudinal'.
(b) Served by a nerve fibre plexus - Auerbach's myenteric plexus, whose parasympathetic ganglion cells lie between the muscle layers.
(c) Circular coat is more developed at sphincters and valves.

4 GI serosa or adventitia/fibrosa (outermost)

(a) Of loose CT, with collagen and elastic fibres, nerves and vessels.
(b) The serosa has a smooth mesothelial covering, and that part of the tract is suspended on a mesothelium-covered tissue fold - omentum or mesentery.
(c) Mesothelial cells bear microvilli, are well attached, and secrete lubricants to allow viscera to move freely.
To avoid knots and obstruction, the plan for the GI tract is fasten, loosen, fasten, and so forth, so that only the small intestine and transverse colon have long stretches of mobile tube: fastening requires an adventitia, mobility, a serosa.

Oesophagus

1 Mucosa has stratified squamous epithelium ending sharply, but along a jagged line, at the gastric junction, creating a white-red distinction between proximal and distal sides of the Z-line in endoscopy. Here, abnormalities of the oesophageal epithelium and the position of the epithelial junction are quite common - Barrett's oesophagus, where the stratified squamous epithelium is replaced metaplastically by simple columnar epithelium with some or all of the small-intestinal cell types.
2 Muscularis mucosae - longitudinal smooth muscle.
3 Cardiac glands - make neutral mucus and are branched tubular, in the mucosa near the gastric cardia, and in mucosa of the upper oesophagus; inconsistently present.
4 Oesophageal glands - acidic mucous, compound, tubulo-alveolar, and lying in the submucosa, less numerous in the middle segment of the oesophagus.
5 Circular and longitudinal external muscle coats of skeletal muscle in the upper fifth or so give way progressively to only smooth muscle in the lower half.
6 Outermost coat is CT adventitia, except on a small piece below the diaphragm.
7 Function - rapid passage of food to (and from) the stomach.

Stomach

(a) Anatomical regions - cardia, fundus, corpus, pyloric antrum and pyloric canal: the regions are histologically distinct.
(b) Outer covering is a serosa, from which hang omenta.
(c) Muscular coat of three smooth muscle layers - outer, longitudinal; middle, circular; inner, oblique. The middle layer is more developed to form a sphincter at the pylorus. The muscle churns the contents (chyme), and passes them periodically in regulated

amounts to the duodenum.
(d) Submucosa - no glands; CT carries vessels and the nerve plexus.
(e) Muscularis mucosae - two layers, with the inner circular one sending a few muscle fibres up towards the lumen.
(f) Mucosa is deep and glandular, with only a little lamina propria tissue; produces acid and enzymes for digestion, and undertakes some absorption, e.g., of water and alcohol.

Stomach mucosa

(a) Empty stomach's lining is folded in ridges - rugae.
(b) Surface is pitted by recesses - gastric pits/foveolae gastricae.
(c) Long tubular glands extend from the muscularis mucosae up to empty into the pits. A gland has a base, neck and isthmus.
(d) The surface of the stomach and the pits are lined by simple, columnar, special mucous epithelial cells.
(e) Gastric glands throughout the body and fundus of the stomach are simple, branched tubules with these cells:

- Chief/zymogenic/peptic serous cells: in the majority; basophilic, with 'zymogen' granules and rich granular ER.
- Parietal/oxyntic cells: occur peripherally and singly; large and eosinophil; packed with mitochondria and smooth ER; have long secretory canaliculi, lined by microvilli, and opening to the gland's lumen.
- Mucous neck cells: concentrated near the neck of the gland.
- Endocrine/enteroendocrine/argentaffin/enterochromaffin/ Kultschitsky cells: few in number, seen with EM, silver methods, or cytochemistry, but may be recognized from their empty look with H & E, and their rarity.

(f) In the narrow cardiac region lie cardiac glands - compound tubular, with mucous and a few parietal cells.
(g) In the pylorus, pits are much deeper, and glandular tubules are wider and more branching. The main kind of glandular cell present is pale and resembles fundic mucous neck cells.

Gastric secretions and cell types responsible

(a) Surface mucous cells - mucus, to prevent auto-digestion of the mucosa, and bicarbonate ions held in the mucus.
(b) Chief/zymogenic cells - enzymes, e.g., pepsin, rennin, gastric lipase.
(c) Oxyntic/parietal cells - Cl^-/HCO_3^- is exchanged basolaterally to balance the apical Na^+/H^+ proton pump used to form the hydrochloric acid of the digestive juice.
(The stimulated active parietal cell has greatly extended canaliculi.)
(d) Mucous neck cells - mucus and enzymes, e.g., dipeptidases.
(e) Endocrine cells - hormones and amines; e.g., a hormone - gastrin - produced by the pyloric antral G cells controls the release and formation of acid from parietal cells, and of digestive enzymes from chief cells.
(f) Parietal cells - intrinsic factor - to assist in the absorption of vitamin B_{12}: this role is upset when the parietal cells' proton pump is an autoimmune target in pernicious anaemia, leading to the cells' destruction.

Gastric protective mechanisms

(a) Digestive secretions (survived by typhoid and other bacilli, and eggs of parasites, which do their damage in the gut, and by Helicobacter pylori). H. pylori, resident in many stomachs, may cause intestinal metaplasia - a pre-malignant state - or peptic/gastric ulcers, in some people.
(b) Mucous and bicarbonate outer coating of the epithelium.
(c) A film of surfactant-like lipid secreted by the epithelium.
(c) Regenerative power of the epithelium, by cell proliferation and migration (normally renewed every few days).
(d) Lymphoid nodules and lymphocytes, and other leucocytes, in the mucosa and submucosa.
(e) Tight junctions between the epithelial cells.
(f) Vomiting.

Small intestine

(a) Three regions - duodenum, jejunum and ileum, anatomically and histologically distinguishable.
(b) Serous coat over all except part of the duodenum and the terminal ileum, which are fixed to the abdominal wall.
(c) Suspended on a mesentery carrying blood and lymphatic vessels, lymph nodes and nerves.
(d) Muscularis externa has two complete layers.
(e) Submucosa - occupied by Brunner's mucous, compound tubular glands in the duodenum; elsewhere is CT as for the rest of the tract.
(f) Muscularis mucosae - inner, circular, and outer, longitudinal smooth muscle.
(g) Mucosa has:
.. (i) Villi - finger- or leaf-like projections.
.. (ii) Crypts of Lieberkühn - simple tubular

○ **Cytology of small-intestinal mucosa**
(a) Enterocytes are columnar absorptive epithelial cells on the villi; with a brush border (many microvilli); are held apically by junctional complexes; the many vesicles at the base of the microvilli communicate with agranular ER.
(b) Goblet cells, with the nucleus, GER and Golgi apparatus basally, stored mucigen droplets apically.
(c) Paneth cells, with eosinophil granules holding defensin and enzymes; remain at the base of the crypts.
(d) Enteroendocrine cells with hormone- and serotonin-containing basal granules.
(e) Undifferentiated columnar crypt stem cells: few microvilli; able to divide, migrate, differentiate into the other kinds, function, and be extruded at the villus tip, over approximately four days.
(f) Villus core has the basal lamina for the epithelium, a central lymphatic capillary (lacteal), blood vessels, smooth muscle fibres. The loose stroma of reticular and elastic fibres is heavily infiltrated by WBCs, e.g., CD4+ helper-inducer lymphocytes and eosinophils, and plasma cells.
(g) Ileum has Peyer's patches of extensive lymphoid tissue, erasing villi, breaking into the epithelium, and interrupting the muscularis mucosae to invade the submucosa. Elsewhere, only solitary lymphoid nodules are to be seen. The

glands. .. (iii) Lamina propria forming the core of each villus and lying between the gland tubules. .. (iv) Covering of simple columnar epithelium.	epithelium domed over the Peyer's-patch follicles is specialized, with M cells, which transport antigen and otherwise assist immune functions.

Functions of small-intestinal mucosa	Devices for increasing area for absorption
(a) Secretory .. (i) Goblet cells give mucus. .. (ii) Columnar cells make disaccharidases and other digestive enzymes .. (iii) Paneth cells form defensins, etc, for defence. .. (iv) Endocrine cells produce hormones to coordinate the functions of the gut, liver and pancreas. .. (v) Simple tubular intestinal glands/glands of Lieberkühn also contribute to the enteric juice.	.. (a) the long length of the gut; .. (b) villi; .. (c) microvilli on absorbing cells; .. (d) plicae circulares/valves of Kerckring (high folds of mucosa and submucosa) .. (e) contractions of villus muscle, muscularis mucosae, and two main muscle coats; (microvilli can slowly elongate, but not contract and relax.)

Changes within small intestine during descent	Protective mechanisms of the gut
(a) Goblet cells increase in number. (b) Villi become more finger-like. (c) Lymphoid tissue increases. (d) Plicae circulares diminish.	(a) alkaline mucus of Brunner's glands; (b) lubricating and protective goblet-cell mucus; (c) immune responses by APCs, lymphocytes and plasma cells; (d) rapid reactions of eosinophils, macrophages, and neutrophils (e) lysozyme and other antimicrobial contributions of Paneth cells; (f) barrier of tight junctions between the enterocytes; (g) diarrhoea; (h) rapid regeneration by the epithelium.

Large intestine

(a) Crypts, but no villi or plicae circulares.
(b) Columnar epithelial cells are: (i) undifferentiated; (ii) goblet (numerous); (iii) colonocytes, absorbing, with microvilli, for water, and some products of bacterial metabolism of the faeces; (some excretion occurs). Endocrine cells are also present.
(c) Dehydrating faeces need lubrication, hence many goblet cells are present in the simple columnar epithelium.

Regional details of large intestine

(a) Colon and caecum: outer longitudinal muscle coat is gathered into three bands - taeniae coli - which pucker or sacculate the tube, forming haustrations. **(b) Appendix:** continuous muscle coats; few crypts; the mucosa is mainly occupied by lymphoid tissue; the muscularis mucosae may be deficient and lymphoid tissue seen in the submucosa. The wall may be thick. With age the lumen may be blocked off/occluded by fibrosis. **(c) Rectum:** outer longitudinal muscle is one continuous sheet.	**(d) Anal canal** .. (i) Morgagni's anal columns are 6-10 vertical mucosal folds. .. (ii) Dentate line lies at the level of the bases of the columns, where there are tiny flaps and pockets - anal valves and sinuses. .. (iii) The histological epithelial anal transitional zone (ATZ) lies between unbroken simple columnar colo-rectal epithelium and lower stratified squamous epithelium. .. (iv) The ATZ - the common site of anal cancers - is very variable in its extent and outline, in its kinds of epithelia, and the number of crypts. .. (v) Submucosal veins display periodic dilations. Deterioration of their supporting connective tissue permits enlargement and prolapse - haemorrhoids. .. (vi) The complex anal musculature includes external skeletal-muscle and internal smooth-muscle sphincters. (The muscles and their innervation are particularly at risk of stretching and damage in women giving birth.)

PANCREAS

- This gland combines exocrine and endocrine functions. The exocrine secretion passes via the duct of Wirsung (and any accessory duct) into the duodenum for digestive and neutralizing purposes.

1 Elongated, lobulated, compound, acinar gland, with a very thin CT capsule and septa.
2 Long duct system and its CT provide support.
3 Exocrine part is major with very many serous acini and some ducts.
4 Endocrine part is minor: many small clusters of cells staining palely (with HE) - islets of Langerhans.

Exocrine pancreas

Acinar structure	Ducts
1 Pyramidal epithelial cells line the acini; are rich in basal granular ER (deeply basophil); have a prominent supranuclear Golgi complex and apical zymogen granules (precursors of several digestive enzymes). 2 Electron-radioautography with labelled leucine showed the secretory pathway through the cell and its time aspects	1 Commence as narrow intercalated ducts within the acini, although vagaries of section plane result in one finding centroacinar cells in only some acini. 2 Beyond the intercalated ducts, ducts have pale cuboidal cells, with few organelles and some microvilli, changing to columnar epithelial cells in the larger ducts. 3 Ducts are less often seen than in the serous parotid gland, and probably actively change the secretions only in the smaller, early ducts.

3 A pale duct cell (or a pair) may be seen intruded into the centre of the acinus as a centroacinar cell.	4 Ducts are accompanied by less connective tissue than in the salivary glands, which are exposed to masticatory forces.

Exocrine function

1 Formation of alkaline secretions, which counter the gastric fluid's acidity, thereby activating pancreatric pro-enzymes for digestion.
2 The release of alkaline and enzymatic secretions is under the hormonal control of secretin, and cholecystokinin/CCK, respectively.

Endocrine pancreas: Islet structure and functions

1 No ducts, but rich in capillaries with a fenestrated endothelium.
2 Pale cells contain granules differing in alcohol-solubility and staining characteristics (distinguishable also in EM and immunocytochemically) for the differentiation of:
(a) Alpha cells, 20 per cent, and large - produce the hormone, glucagon, which raises the blood's glucose level.
(b) Beta cells, 75 per cent, smaller - produce insulin, which promotes the intracellular movement of glucose and glycogen storage, thereby lowering the glucose level of the blood.
(c) Delta cells, 5 per cent, with large argyrophil granules; form somatostatin, which inhibits insulin and glucagon release.
(d) F cells/PP cells, in islets and among exocrine cells, making pancreatic polypeptide (PP), acting centrally on the brainstem to influence the vagal control of GI functions, and on the liver.
3 Blood drained from the pancreas and bearing the polypeptide hormones passes, via the portal flow, to the liver.

LIVER AND GALLBLADDER

Liver's general features

1 Large, lobated exocrine and blood-processing gland, with 2 vessels and ducts entering and leaving at the porta. 3 Enclosed by a thin CT capsule, mostly covered by mesothelium. 4 CT of the branching vascular system provides gross support. 5 Parenchymal cells are supported by fine reticular fibres.	6 The internal structure is understandable in terms of the several vessels entering or leaving the organ; (a) Portal vein bringing food-rich blood from the gut. (b) Hepatic artery bringing arterial blood. (c) Hepatic veins taking away processed blood into the vena cava. (d) Lymphatics taking away some lymph. (e) Hepatic ducts removing bile to the gallbladder and gut.

Liver lobule

1 First impression is of a uniform mass of large glandular cells throughout the liver substance. 2 Closer examination shows that the cells are arranged in perforated plates, one cell wide. Between the plates are sinusoidal blood channels 9-12 µm wide, lined by endothelial cells. 3 Scattered in the glandular mass are blood vessels, alone and accompanied by other vessels. 4 The distribution of these vessels defines or marks out the classic hepatic lobules.	**5 Varieties of liver vessel** • Central vein/terminal hepatic venule - very thin wall; lies in the centre of a lobule, with sinusoids converging towards and opening into it. • Sublobular/intercalated vein - thicker wall; lies alone at the periphery of the lobule. • Branch of portal vein - again at the periphery of the lobule, but accompanied by one or more small hepatic arteries/arterioles, one or more bile ducts/ductules lined by cuboidal epithelium, and lymphatics. Vein, artery, and bile duct constitute a portal triad; the area in which they lie is a portal area/canal.

6 In pig and camel, the lobules are separated from one another by CT and thus much more easily identified.
7 Hepatic lobular blood flow is:
(a) from branches of the portal vein and hepatic artery; from the periphery towards the centre;
(b) in the sinusoids, between the cell plates.
(c) Blood collected in central veins goes to sublobular veins, thence to collecting veins, and then hepatic veins leaving the liver.
8 Intralobular bile flow is from the lobule's centre towards the peripheral bile ducts, and runs, within any one cell plate, between the liver cells in bile canaliculi.

Rappaport's liver acinus

- A functional unit comprising parts of three or so lobules. It sought to account for differences in exposure to the blood supply among various parts of lobules.
- Such differences are reflected in varied functional activities and degrees of susceptibility to toxic agents - a metabolic zonation
- The territory of an acinus has, as its axis, one final branch of the portal vein, and is subdivided into: 1 periportal, 2 intermediate, and 3 perivenous (close to the central vein) zones, with the initial periportal zone being roughly spheroid, and isolated from periportal zones of adjacent acini.
- The concept is not easy for students to follow, nor, it seems, for hepatocytes, which, for many processes, heed different patterns. To best fit events to the architecture, hepatologists are now more likely to employ the simpler concept of separately continuous periportal and perivenous/pericentral zones, than that of discrete acini.

Liver sinusoids

1 Are lined by fenestrated endothelial cells, loosely attached, and hold
2 phagocytic Kupffer cells (larger, stellate, with a pale oval nucleus), demonstrated by the vital intravascular injection of trypan blue or carbon particles, or latex particles for microscopy in vivo.
3 Fenestrated lining cells are not tightly attached and rest on microvilli of underlying hepatic cells, without a BL intervening.
4 Plasma can thus pass through the sieve plate, formed by the lining cells, out into the perisinusoidal space of Disse to interact with the hepatocytes. Some of this fluid may pass to the periphery of the lobule to be collected as lymph.
5 Disse's 'space' contains ECM materials, but not a visible basal lamina.
6 Scarce, fat-storing, stellate cells of Ito lie outside the endothelial cells. They store vitamin A. They respond to a variety of insults by making collagen and causing cirrhosis (fibrosis).
7 The sinusoidal wall provides for:
.. (a) blood cleansing, e.g., of gut bacterial toxins;
.. (b) haemopoiesis in the embryo;
.. (c) bringing plasma into intimate contact with the hepatic cell for its many metabolic functions of storage, transformations, syntheses, regulation of plasma concentrations, detoxifications, the production of bile, and assisting defence by producing acute-phase proteins.

Hepatocyte/hepatic cell

- Large, polyhedral, 30 µm x 20 µm cell with:
- large, spheroid nucleus (sometimes two), with membrane pores, and ribosomes on the outer membrane
- cell membrane projecting microvilli into the space of Disse, and held firmly to adjacent cells, especially around the channel, the bile canaliculus, formed by the separation of two or three cells' membranes and equipped with a few microvilli;
- lycogen granules stored in association with smooth ER (an association seen elsewhere);
- fat droplets occurring briefly after meals;
- lipofuscin or aging pigment, as another normal inclusion; and sometimes brown haemosiderin, with its iron, may be seen.

Bile pathways

1 System of canaliculi between the hepatic cells leads to
2 canals of Hering/cholangioles, with both hepatocytes and pale duct cells in their walls. Next come, in the portal areas,
3 bile ductules with only small, pale cuboidal cells, firmly held by membrane interdigitations and junctional complexes, and having a few luminal microvilli.
4 Bile ducts' epithelium changes to columnar mucous cells and, extrahepatically, the ducts acquire smooth muscle as well as CT.
5 Cystic duct allows reflux into the gallbladder, when Boyden's sphincter choledochus at the duodenal outlet of the common bile duct is closed.

Gallbladder

1 Extensively folded mucosa of tall, simple, columnar epithelial cells with many microvilli, lying on a loose lamina propria.
2 Goblet cells are absent, but in the neck there may be small glands of uncertain function.
3 The middle layer has variously disposed (mainly circular) smooth muscle bundles.
4 Outermost is a serosa of mesothelium-covered areolar CT with vessels and nerves, except where the gallbladder attaches to the liver.
5 Function - stores and concentrates the bile by actively absorbing sodium, coupled with water and anions.

22- HYPOPHYSIS/PITUITARY GLAND

1 Linked by a stalk to the base of the brain, and lies surrounded by dural membrane (capsule) in the bony sella turcica.
2 Stalk extends through the dural diaphragma sellae. Pituitary weighs 0.5-l.0 g.
3 Divisions of the pituitary gland

4 Embryological origins
- Adenohypophysis develops from the ectodermal Rathke's pouch above the oral cavity.
- Rostral wall of Rathke's pouch becomes the anterior lobe; caudal wall gives the intermediate lobe; the cleft between the intermediate and anterior lobes occludes to a line of cysts; and the dorsolateral corners of the pouch give the pars tuberalis.
- Neurohypophysis comes as a downgrowth of the floor of the diencephalon. The brain connection is maintained.

Adenohypophysis (histology and function)

1 Pars tuberalis - wrapped around the neural stalk are cords of basophilic cells containing gonadotrophic hormones.
2 Pars intermedia - rudimentary in man; variable in width; several colloid-filled cysts; glandular cells - chromophobe or basophil; basophilic cells may extend into the neural lobe; function - unknown in man, but in fish and amphibia the melanocyte stimulating hormone (MSH) formed varies skin pigmentation.
3 Pars distalis
(a) Thick, branching cords and plates of cells, supported on basal laminae and reticular fibres. Between the cords run wide sinusoidal capillaries of fenestrated endothelial cells on their own BLs.
(b) Classical division of the cells was into acidophils (40 per cent), basophils (l0 per cent), and chromophobes (50 per cent).
(d) Chromophils can be distinguished by various stains, since some form peptide hormones, others glycoproteins; by EM, from the size, density and shape of the granules; and by immunostaining, for LM and EM.
(i) ACIDOPHILS: Somatotroph - makes growth hormone (GH)/somatotrophin (STH); stained by orange-G
Lactotroph/Mammotroph - makes prolactin/mammotrophin (MTH); stained by erythrosin
(ii) BASOPHILS, staining also with PAS and aniline blue
Thyrotroph gives thyrotrophic hormone (TSH/TH)
Gonadotroph gives luteinizing hormone (LH) and follicle-stimulating hormone (FSH)/interstitial cell-stimulating hormone (ICSH)

(c) Chromophobes are sparsely granular, small, pale, and often clustered together. They are thought to be less active forms of the five secretory, granular, chromophil cell kinds.

Corticotroph makes adrenocorticotrophin (ACTH) by cleaving pro-opiomelanocortin (POMC) appropriately

Hypothalamic regulation

- Hypothalamic regulation of the adenohypophysis is via the hypothalamo-hypophyseal portal circulation, and for gonadotrophins, ACTH, and TSH, functions by negative feedback thus:
  1. Hypothalamic neurons are specialized to be sensitive to a blood deficiency of the target gland's hormone, e.g. thyroxine.
  2. From the sensitive neuron's terminal, a neurosecretory, chemical peptide releasing factor, e.g. TH-RH/TH-RF, passes into
  3. blood capillaries of the median eminence, whence it drains down
  4. via the portal circulation to the pars distalis.
  5. The releasing factor passes out of the blood to activate the appropriate
  6. chromophil cell, which produces more trophic hormone, TH.
  7. The trophic hormone passing in the blood to the target gland, thyroid,
  8. promotes an increased output of target gland hormone, thyroxine, whose raised blood level
  9. then reduces the activity of 1. the sensitive hypothalamic neurons, i.e., the system uses a negative feedback.
- This simplification ignores the inhibitory factors, such as hypothalamic somatostatin preventing the release of growth hormone.

Neurohypophysis

- May be viewed as a downward extension of the hypothalamus, allowing for hormone storage and a complete breach of the blood-brain barrier for hormone release. Its structure follows:

1 The neural stalk and posterior lobe consist of the unmyelinated axons (grouped as the hypothalamo-hypophyseal tract)
2 of neurosecretory neurons of the hypothalamic supraoptic and paraventricular nuclei.
3 The neurosecretion collects, and dilates some axons and their terminals into Herring bodies. Gomori staining or EM shows the presence of granules in these axons, but not in the
4 pituicytes - a neuroglial kind of cell.
5 The secretion collects in terminals arranged as a palisade around blood vessels. Its release may involve electrical discharge in the axon and chemical factors in the 'synaptic' vesicles also present.
6 Two polypeptide hormones in the secretion are:
(a) oxytocin/pitocin: makes mammary gland myoepithelial cells and uterine smooth muscle contract;
(b) vasopressin/pitressin/antidiuretic hormone (ADH): makes the kidney collecting tubule permeable to water, and influences vascular and gut smooth muscle.
7 The neural lobe has a direct arterial supply from the inferior hypophyseal arteries to its fenestrated capillaries.

PINEAL GLAND/EPIPHYSIS CEREBRI

1 Originates as a dorsal outgrowth at the caudal end of the diencephalon. Unlike the pituitary, it is not connected directly by nerve fibres with the CNS.
2 The capsule of pia extends in septa to lobulate the organ, and carry in extensive blood vessels.
3 There is a regulatory autonomic nerve supply via the superior cervical ganglia.
4 Constituent cells
(a) Pinealocytes: basophilic, with secretory inclusions and lipid droplets; nuclei indented; many ribosomes and smooth ER; innervated by sympathetic fibres; and release melatonin.
(b) Interstitial glial cells: 5 per cent; stellate with long processes.
5 Increasing in number throughout life are mineral concretions - so-called brain sand (acervuli cerebri/corpora arenacea).
6 The pineal is responsive to changes in environmental light, initially mediated via the accessory optic tract and the suprachiasmatic nucleus.
Darkness raises the production of the enzyme hydroxyindole-O-methyl transferase (HIOMT), which methylates N-acetyl-serotonin to give melatonin.
7 Melatonin is part of the internal clock, matching the rhythm of alertness, and gonadal and other endocrine functions, to external light-based circadian and seasonal cycles. (In amphibia, melatonin also reduces the dispersal of pigment within melanocytes, hence the name.)

THYROID GLAND

1 Develops from an endodermal downgrowth at the base of the tongue. The thyroglossal duct, connecting it with its point of origin, later disappears. Two lateral lobes, an isthmus (and sometimes a pyramidal lobe) are established.
2 The inner, true, CT capsule sends in septa to partially enclose lobules.
3 In the lobules are rounded or elongated bodies - follicles, in a loose stroma of CT, with many blood vessels.

Thyroid follicle

l In man, they vary between 0.02 and 0.9 mm in diameter. A gland has several million follicles.
2 Filled with viscous fluid - thyroid colloid - variably acidophil or basophil, and often shrunken and showing knife chatters.

- **Thyroid histophysiology**
- **C Cells**

(a) Are APUD cells of neural crest origin,
(b) and produce the polypeptide calcitonin for the reduction of high plasma Ca^{2+} and phosphate levels.
(c) Although diffuse, in sum they form a gland antagonistic to the action of the parathyroids.

- **2 Follicular cells**

(a) Are stimulated by pituitary thyrotrophic hormone (TSH) to produce and release two iodinated amino-acid hormones - tetraiodo-thyronine (thyroxine/T4) and 3,5,3-triodo-L-thyronine(T3),
(b) which are stored in the colloid, as component amino acids of the glycoprotein - thyroglobulin.
(c) The hormones accelerate general and specific metabolic processes of the body.
(d) Electron radioautography has shown the sites in the sequence of

3 Lined by basophilic cuboidal follicular cells, varying in height as a simple epithelium on
4 a basal lamina, outside which is an extensive plexus of blood capillaries, and reticular fibres and fibroblasts.
5 Follicular cells are polarized with respect to the follicle lumen; the nucleus is central, the Golgi complex supranuclear; EM shows plenty of granular ER, some luminal microvilli, endocytotic vesicles, and lysosomes.
6 Between the follicular cells and the BL, and sometimes outside the BLs, lie occasional C cells (clear/parafollicular cells), having no direct access to the lumen, and no colloid droplets, but with small argyrophil, secretory granules.

hormone production by the follicular cells:
(i) Iodide concentration - basal part of the follicular cell.
(ii) Iodide oxidation - throughout the cell.
(iii) Synthesis of thyroglobulin - basal cell, granular ER, Golgi body, by vesicle to the lumen.
(iv) In the luminal thyroglobulin, tyrosine residues are iodinated, then pairs condense.
(v) Cellular retrieval of thyroglobulin from colloid storage - cell's apical region by endocytosis.
(vi) Transport to lysosomes, where cathepsins degrade the large modified molecule.
(vii) Release of freed iodothyronines - out of the base of the cells into the blood.

PARATHYROID GLANDS

1 Derived embryologically from the 3rd and 4th pharyngeal pouches.
2 Adherent to the true capsule of the thyroid.
3 Each of the four or more rounded or ovoid bodies has a fine CT capsule and delicate, incomplete septa.
4 These septa carry vessels, nerves and many fat cells.

Histophysiology

1 Supported on fine reticular fibres are many fenestrated blood capillaries and sheets and cords of
2 glandular cells:
(a) Chief cells: small, 7-l0 µm diameter; some dark, some light: contain glycogen, a Golgi complex, lipofuscin pigment, and argyrophil secretory granules; form occasional small follicles.
(b) Oxyphil cells; larger, acidophilic, and often occur in clumps; cytoplasm is packed with mitochondria; no secretory granules; serve no known role. More oxyphil cells are seen in older individuals.

Functions

(a) Secretory granules of chief cells are the polypeptide hormone, parathormone/PTH, released in response to low blood Ca^{2+}, and acting on osteoclasts and macrophages to increase bone resorption.
(b) In the kidney, PTH: promotes the tubular reabsorption of calcium, and the 1, activation of vitamin D; and inhibits the renal tubular reabsorption of phosphate - a phosphaturic action.
(c) Unlike most other endocrine glands, no specific pituitary trophic hormone is involved in its control.

ADRENAL/SUPRARENAL GLAND

1 Elongated glands of cocked-hat or crescentic shape.
2 Composite of medullary and cortical tissues, linked by blood supply, but embryologically and functionally distinct.
3 Mesodermal cells of coelomic mesothelium differentiate into:
(i) inner, provisional or fetal cortex (involutes at birth); and
(ii) outer, permanent cortex.
4 Neural crest ectodermal cells migrate: (i) to coeliac ganglion; and (ii) then some go beyond to invade the adrenal cortical tissue and form the medulla.
5 Mature adrenal has a thick CT capsule, bringing arteries to serve radial capillaries draining down towards the venules and central vein of the medulla. Arterioles also penetrate the cortex to serve a medullary capillary bed.
6 The medulla is a long, thin strip of basophilic cells, which can be made outstanding by the chromaffin reaction - a darkening produced by dichromate ions.
7 The supporting element throughout is the reticular fibre.

Cortex

1 Polyhedral glandular cells, in cords usually two cells wide, run roughly radially, along with sinusoidal capillaries.
2 Three layers are visible:
- (a) Zona glomerulosa - under the capsule, rounded balls or groups of columnar cells with dark nuclei.
- (b) Zona fasciculata - long, straight cords of large cells, swollen with lipid droplets.
- (c) Zona reticularis - network made up of cells, small and often lipid-free; lies nearest to the medulla.

3 Lipid droplets (Sudanophilic and osmiophilic) contain cholesterol and cholesterol esters, used in conjunction with the Golgi body, smooth ER and special mitochondria, to produce two kinds of
4 steroid hormones: mineralo- and gluco-corticoids. Examples:
(a) Aldosterone (mineralo-corticoid) helps control water and electrolyte balance, e.g., by promoting renal Na^+ reabsorption, and having repercussions on blood pressure; secreted in the Z. glomerulosa, and released in response to angiotensin II.
(b) Cortisol (gluco-corticoid) helps control carbohydrate metabolism, e.g., facilitates protein catabolism and gluconeogenesis (thus interfering with processes requiring a high rate of protein synthesis, such as wound repair and antibody responses): formed in Z. fasciculata and reticularis in response to pituitary ACTH, itself released under hypothalamic control; glucocorticoids affect the cells and ground substances of connective tissues.
(c) Other glucocorticoids, and significant amounts of sex hormones, in Z. Fasciculata and reticularis.

Medulla

1 Two cell kinds:
(a) Sparse ganglion nerve cells, probably serving vascular smooth muscle in arterioles and the central vein.

4 The hormones are stored in characteristic membrane-bound granules, visible in EM. The granules form in

(b) Chromaffin cells: large, granular, and arranged around venules, with their other pole by blood capillaries; by far the major cell type.
(c) Schwann cells to accompany the nerve fibers.
2 Release is controlled by a direct, 'preganglionic', sympathetic innervation, terminating synaptically on the glandular cells.
3 The hormones released are:
(a) Norepinephrine (transmitter substance for sympathetic, postganglionic fibres).
(b) Epinephrine (increases cell respiration, cardiac output, and glucose mobilization, for the great muscular effort needed in fighting or fleeing).

relation to the Golgi body, but a dense GER is not required. They also contain enkephalins and chromogranin.
5 Both principal hormones are catecholamines, which can be converted by oxidizing agents, e.g., dichromate or ferric salts, to brown-coloured polymers - adrenochromes: this is the chromaffin reaction.

KIDNEY

The kidney is not only the target for hormones, but it also makes several.
l Renin is an enzyme, formed in the juxtaglomerular modified muscle cells, that acts on a blood protein to form the potentially hypertensive angiotensin l. One triggering stimulus is the chloride concentration in the distal tubule detected by the macula densa cells.
2 l,25-hydroxycholecaliferol - the active form of vitamin D, needed for the intestinal absorption of Ca^{2+} and some direct actions on bone cells, is made in the kidney. Vitamin D from synthesis in the skin, or from the diet, is changed to 25-HCC in the liver, but the final 1,25 step is a renal task.
3 Erythropoietin is a protein growth factor, made by predominantly medullary renal fibroblasts, that stimulates the production of erythrocytes by marrow, e.g., when the atmospheric O_2 falls at high altitude

APUD NEUROENDOCRINE AND PEPTIDE SYSTEMS

l APUD Within some endocrine glands, chemoreceptors, the brain, and dispersed in epithelia, are cells that form amine compounds. After an **A**mine **P**recursor has been taken **U**p, the cell **D**ecarboxylates it to form serotonin (5-HT) from 5-hydroxytryptophane, or a catecholamine from dihydroxyphenylalanine (hence APUD).

Peripheral	Central
1 Pancreatic islet cells -> insulin, glucagon, and somatostatin 2 Thyroid C cells -> calcitonin 3 Parathyroid chief cells -> parathormone 4 Gastrointestinal endocrine cells -> gastrin, secretin, pancreozymin/ cholecystokinin, glucagon, motilin, somatostatin, and many other active peptides. (Cells have a designating letter, if the hormone is known). 5 Other endocrine/neuroendocrine cells in respiratory and genito-urinary tract epithelia hold granules, reacting with silver salts in the argyrophilic and argentaffin ways of the GI-tract endocrine cells, and produce a variety of peptides,:VIP.	5 Pituitary .. somatotrophs -> growth howmone (GH) .. mammotrophs -> prolactin (PRL/MTH) .. corticotrophs -> adrenocorticotrophic hormone (ACTH) .. melanotrophs -> melanocyte-stimulating hormone (MSH) 6 Hypothalamic large neurosecretory cells -> oxytocin, vasopressin 7 Hypothalamic small neurosecretory cells -> releasing factors/hormones, e.g., LH.RF; and somatostatin (SRIF) inhibiting GH release from pituitary somatotrophs. 8 Pinealocytes -> melatonin

23- MALE REPRODUCTIVE SYSTEM

- Male reproductive organs form spermatozoa, suspend them in secretions produced by accessory glands, and conduct them, via seminal pathways, to the female reproductive tract by mating behaviour.
- These activities are influenced by hormones, including ones formed by the testes.

TESTIS

1 Very dense CT capsule - tunica albuginea, with an outer mesothelium-covered visceral tunica vaginalis propria.
2 Septa/septula extend from the capsule to the CT mediastinum.
3 In the partitions thus formed (lobuli testis), lie looped, coiled seminiferous tubules, lined by germinal epithelium, and feeding via straight
4 tubuli recti into cuboidal epithelium-lined ducts of the
5 rete testis, which lead through the mediastinum to roughly 6-12
6 ductuli efferentes. These take the spermatozoa to a
7 single, coiled, tubular epididymis lying behind the testis.
8 Between, and outside, the coils of a seminiferous tubule lie blood and lymph capillaries, cells and fibres of CT, and hormone-secreting Leydig interstitial cells.
9 The testis is a mixed endocrine and compound, tubular, cytogenic exocrine gland.

Seminiferous tubule and spermatogenesis

1 The tubule has a substantial support of the basal lamina, plus two or more alternating layers of collagen fibres and muscle-like/myoid cells, with adherent external lamina.
2 The stratified germinal epithelium has cells of two kinds:
(a) spermatogenic cells, quiescent or in the various phases of development;
(b) Sertoli supporting cells; well attached, tall with an irregular columnar form, and a pale ovoid nucleus with a prominent nucleolus; taking up testosterone; and controlling spermatogenesis.
3 Spermatogenesis in the epithelium is initiated by the pituitary hormone FSH, and passes through these stages:

4 Spermatogenesis is vulnerable to heat, X-rays, dietary deficiencies, pesticides, and other poisons. Conventional microscopy reveals defects in sperm shape and motility, leading to infertility. FISH and other molecular techniques are needed to assess genetic damage, sometimes arising during meiosis.
- Spermatogenesis is protected to a degree by the tight attachments

(a) spermatogonium, spheroid cell lying basally, divides mitotically for several generations, then become a
(b) primary spermatocyte, larger, divides by the first meiotic division (to halve the chromosome number to haploid 23 and introduce genetic variety), to produce
(c) secondary spermatocytes, small, soon undergoing the second meiotic division, maintaining the chromosome number at 23, to give
(d) spermatids, smaller and incompletely separated, which, without dividing, metamorphose by the process - spermiogenesis - into
(e) spermatozoa, released into the tubule's lumen.

between the capillary endothelial cells and, separately, between the Sertoli cells, creating a two-tiered blood-testis barrier, for example, against immune attack. The inner protected compartment of the seminiferous tubule is the 'adluminal' compartment.

5 The **spermatozoon** is a very elongated motile cell, with a cell membrane enclosing the:
(a) acrosomal head cap, with an enzyme - proacrosin - to aid binding to, and penetration of, the zona pellucida of the oocyte;
(b) nucleus, streamlined in shape, with dense chromatin;
(c) neck joining the head (nucleus and head cap) to the flagellar tail, which has the:
(i) middle piece, with an axial axonemal core of microtubules in a cilium-like array, nine dense longitudinal fibres and, outermost, a sheath of mitochondria ending at the annulus;
(ii) principal piece, with both longitudinal and circumferential fibres around the axoneme;
(iii) end piece, with microtubules like a cilium, but no dense fibres.

6 Spermiogenesis - whereby the spermatid, a typical cell (except for its chromosomes) becomes a spermatozoon - involves:
(a) construction of the acrosome by the Golgi complex;
(b) the nucleus, thus polarized at one end, condenses and elongates;
(c) at the other end, one of the centrioles initiates formation of the flagellar tail;
(d) mitochondria migrate to form a sheath in the tail;
(e) excess cytoplasm is shed as a residual body;
(f) the head of the spermatid throughout spermiogenesis stays held in a recess in a Sertoli cell.

7 Sertoli cell functions: to protect, nourish, and release the spermatids; to phagocytose residual bodies; and to make androgen-binding protein, fluid, and inhibin to influence pituitary FSH release.

Endocrine testis

1 Leydig cells, eosinophilic, with much smooth ER, lipid droplets, and crystals of Reinke, lie outside the tubules' BLs, constituting a diffuse, steroid-secreting endocrine gland.
2 Leydig interstitial cells are controlled by gonadotrophic interstitial cell-stimulating hormone (ICSH/LH) of the anterior pituitary, and produce the androgenic hormone - testosterone, responsible for:
3 (a) spermatogenesis; (b) development and maintenance of reproductive ducts and accessory glands; (c) secondary sexual characteristics; (d) male mating behaviour; (e) general anabolic effects on metabolism.

PATHS TRAVERSED BY SPERMATOZOA

Efferent ducts/Ductuli efferentes

1 Unevenly lined by simple, columnar, epithelial cells, in groups of tall ciliated and short secretory; the wall has circular smooth muscle;
2 functions - reabsorption of the fluid used to move sperm out of the testis; maturation of the sperm.

Epididymis/ductus epididymidis

1 Regularly lined by tall, absorptive, columnar cells with non-motile stereocilia, and smaller basal cells, together forming a pseudostratified epithelium;
2 outside the BL is a little smooth muscle and, between the coils, is a stroma of dense CT with capillaries;
3 functions - as for ductuli efferentes.

Ductus deferens/vas deferens

1 Lined by an epithelium similar to that of the epididymis, on a lamina propria; in the ampulla, this mucosa has many folds;
2 most of the very thick wall is smooth muscle: inner, longitudinal; middle, circular; outer, longitudinal;
3 adventitia of CT binds it to nerves, blood and lymphatic vessels, and the skeletal cremaster muscle, to comprise the spermatic cord;
4 function - rapid transport of sperm during ejaculation, under sympathetic control.

Ejaculatory ducts

1 Each occurs after a dilation of the ductus d. - the ampulla;
2 lined by pseudostratified or simple columnar epithelium on CT, without smooth muscle.
3 Ducts open into the prostatic urethra through a hillock on the posterior urethral wall - verumontanum/colliculus seminalis, with its blind recess - utriculus masculinus.

Urethra

MALE ACCESSORY GLANDS

Prostate gland

1 Lobulated by septa of CT, with much smooth muscle.
2 Divisible, with histology and rectal-probe ultrasound, into several zones:
.. peripheral (prone to cancer),
.. transitional,
.. central,
.. peri-urethral (subject to benign prostatic hypertrophy), and
.. an anterior non-glandular fibromuscular zone.
3 Large-lumened secretory acini are lined by pale columnar or cuboidal epithelial cells, on a BL. Epithelium is patchily pseudostratified, i.e., bearing some small basal cells.

Seminal vesicles

1 Coiled, convoluted, tubular structures; with a
2 very extensively folded mucosa, having
3 a pseudostratified, columnar, secretory epithelium.
4 The wall has circular and longitudinal smooth muscle, and a thin, outer, fibro-elastic adventitia.

4 Acini open into many ducts, entering the urethra individually, thus the prostate is a collection of compound tubuloacinar glands.
5 Laminated, rounded, prostatic concretions (originally glycoprotein, but later calcifying) - corpora amylacea - develop in some acini as age increases.
6 Functions - secretion of a watery fluid to dilute the semen; the protease - prostate-specific antigen (PSA) - liquifies the gel from the seminal vesicles to free the sperm; the roles of the citrate (the anionic counterpart to Na^+) and acid phosphatase are uncertain.
7 The stroma has abundant smooth muscle to make the prostate a self-squeezing gland, without the need for myoepithelial cells. Stroma interacts with the epithelium in the control of growth and secretion, and is a major player in benign prostatic hypertrophy.

5 Functions - secretion of a viscid gel composed of seminogelin, with fructose to provide energy for the sperm, and prostaglandins that may alter contractions in the female tract.

Cowper's bulbo-urethral glands

1 Compound, tubulo-alveolar gland making special mucus, thought to
2 lubricate and prepare the urethra for ejaculation.

PENIS

1 The thin, elastic skin of the shaft is loosely attached.
2 Connective tissue capsules or tunicae albugineae enclose
3 three roughly cylindrical erectile bodies - two corpora cavernosa penis, and one corpus spongiosum/cavernosum urethrae.
4 The two corpora cavernosa are incompletely separated by a sagittal pectiniform septum. Their endothelium-lined venous sinuses, between a meshwork of dense trabeculae of muscular CT, can be engorged with blood from helicine (coiled) arteries causing erection.
5 Corpus spongiosum
(a) is erectile, but less turgid than the corpora cavernosa;
(b) has less smooth muscle in the CT trabeculae;
(c) originates proximally as the bulbus urethrae and
(d) extends distally to form the bulbous glans, occupied by many veins and nervous receptors, and covered by stratified squamous epithelium, variably keratinized;
(e) ensheaths the cavernous/penile urethra, lined by stratified columnar and finally stratified squamous epithelium.

6 Erection and detumescence are controlled by autonomic nerve fibres to the arteries and trabecular smooth muscle. Erection results from parasympathetically directed trabecular and arterial relaxation, and passive occlusion of the veins draining the corpora.
Sensory nerves serve the glans, skin and deep receptors.
7 Functions - urination/micturition; copulation.

24- FEMALE REPRODUCTIVE SYSTEM

- This is a tubular system for the production of ova, and the reception of spermatozoa, their transport and union. It accommodates the fertilized oocyte and ensuing fetus, then expels the fetus at term.
- The ovary and placenta also have hormone-secreting functions, for instance, to prepare the uterine mucosa to receive, accept, and sustain the fertilized oocyte. Mammae are modifications of the skin for feeding the infant.

OVARY

1 Covered by mostly simple epithelium (variably columnar, cuboidal, or squamous),
2 under which is a loose CT, a nominal capsule - tunica albuginea.
3 Has a stroma of atypical fibroblasts; collagen, as reticular fibres, is present, but not a dominant element; and stromal cells secrete hormones.
4 A fold of peritoneum, the mesovarium, connects the ovary at its hilum to the broad ligament, and sends many blood vessels to the fibrous, central, medullary, region of the ovary.
5 Peripheral, cortical, regions have many primordial and primary follicles, maturing Graafian follicles, which shed the ova (to be fertilized in the upper third of the Fallopian tube), and glandular masses.
6 Certain vestigial structures remain after development has ceased. These take the form of blind epithelium-lined tubules - epoöphoron and paroöphoron - lying in the broad ligament by the ovary.
7 Hilar stromal cells may include hormone-secreting hilus cells, resembling testicular Leydig cells, which occasionally give rise to tumours causing a hyperandrogenic syndrome in the woman.

Maturation of oöcyte

(a) Oocyte increases in size.
(b) Golgi complex and other organelles become more dispersed in the cytoplasm, and lipid droplets appear.
(c) Zona pellucida of glycoprotein forms between the oocyte and surrounding follicular cells; both extend processes into it. The zona pellucida may protect the ovulated and fertilized oocyte from phagocytosis and immune rejection.

Development of follicular/granulosa cells and follicle

(a) Follicular cells are present as a single squamous layer, encircling the dormant oocyte (stage of primordial follicle).
(b) The primary follicle arises by enlargement of the follicular cells - they become cuboidal - and of the oocyte.
(c) Follicular cells proliferate to a multilayered state (secondary/ preantral follicle).
(d) Primary oocyte moves to an eccentric position. Fluid forms, separating follicular cells and collecting in antra (spaces). Further cell multiplication, and fluid coalescence, lead to a large follicle, withliquor folliculi filling a single antrum (antral/vesicular/ tertiary/Graafian follicle).
(e) In the follicular lining of granulosa cells, a hillock - cumulus oöphorus - encloses the oocyte.
(f) The granulosa cells synthesize materials for the oocyte, and also oestrogens, and inhibin to reduce FSH release from the pituitary.

Changes in stroma around maturing follicle

(a) Stromal fibroblast cells build a capsular theca, which
(b) differentiates into:
.. (i) an inner theca interna: ovoid secretory cells, with lipid droplets; vascular;

Ovulation

(a) A sudden surge in LH, coupled with an increase in FSH and a peaking oestrogen level, triggers ovulation, after the completion of meiosis I by the oocyte.
(b) Graafian/antral follicle, grown huge (15 mm diameter), extends to

.. (ii) an outer theca externa: fusiform fibroblastic cells packed densely. (c) The growing theca interna secretes androgenic precursors of oestradiol-17b for aromatase-mediated conversion by the granulosa cells. (d) A glassy basal lamina develops between the theca cells and the membrana granulosa lining the follicle.	and protrudes from the ovarian surface. (c) Protruding apical tissue weakens at the stigma, by apoptosis, and enzymatic action on its matrix, and ruptures, helped by thecal cellular contractions; the fluid flows out. (d) The fluid takes with it the already floating secondary oocyte (a first maturation division having recently occurred), and some attached granulosa cells as a corona radiata.

Corpus luteum: formation, function and fate

(a) Burst follicle's wall collapses, becoming folded/plicated. (b) Lining granulosa cells become secretory granulosa lutein cells - the main component of the corpus luteum of menstruation (CLM), or of pregnancy (CLP); theca interna cells become secretory theca lutein cells (found as small nests of darker cells at the periphery of the main mass of granulosa lutein cells, and accompanying vascular septa into the CLM). (c) Lutein cells become enlarged, with many lipid droplets (vacuoles, in H&E preparation) and much smooth ER, and secrete the steroid hormone - progesterone, (d) which is collected in capillaries that grow in from the theca interna.	(e) Progesterone makes the uterine mucosa secretory; and inhibits menstruation and uterine muscle contraction, if implantation occurs. (f) The centre of the collapsed follicle fills with clotted blood, which is reorganized by ingrowing fibroblasts and capillaries to form a pale, central core of CT. (g) Late in pregnancy, or late in the menstrual cycle (if the shed oocyte is not fertilized), the glandular lutein cells degenerate; the corpus luteum shrinks, and is replaced by a small pale mass of hyalinized CT - corpus albicans (white to the naked eye in the fresh, unstained ovary).

FALLOPIAN/UTERINE TUBE (oviduct)

1 Four parts: (a) infundibulum with the fimbria - a fringe of processes, engorgeable with blood and moved by smooth muscle to catch the oocyte, (b) wide ampulla, with a cell-ensnaring labyrinth of protruding mucosal processes, (c) narrow isthmus down to the uterus, and (d) an intramural/ interstitial section through the uterine wall. 2 Lined by a highly folded mucosa, comprising a cellular lamina propria covered by a simple columnar epithelium of 3 columnar ciliated cells, and secretory cells, varying in height and secretory activity during the menstrual cycle. Secretion is more in the late oestrogen phase around ovulation than in the post-ovulatory progesterone phase. Cilia beat toward the uterus.	4 Muscularis of inner, circular, smooth muscle, and a few outer, longitudinal bundles. 5 Covered outside by a serosa, with nerves and blood vessels. 6 Functions - meeting place for sperm and oocyte; helps 'capacitation' of sperm to their most energetic and zona pellucida-penetrating state; nourishes and transports the zygote.

UTERUS

1 Outer serous coat (perimetrium), with vessels, nerves, and ganglia. **2 Myometrium** of interwoven smooth muscle, capable of a great hypertrophy during pregnancy, with many blood vessels in the middle stratum vasculare. **3 Mucosa/endometrium** with: 1 simple, columnar, epithelial lining (some cells ciliated); 2 simple, tubular mucous glands; 3 loose vascular stroma of special fibroblasts, reticular fibres and much ground substance; some stromal cells can become decidual around the implantation site; 4 helicine/coiled spiral arteries, a capillary bed, and veins.	**4 Mucosa** of the sexually mature woman experiences cyclic menstrual changes, involving all elements and considerable changes in mucosal thickness, and driven hormonally by the ovary: 1 Oestrogens, e.g., oestradiol, from the growing follicle cause cell proliferation, and an increase in endometrial height. 2 Progesterone, formed by the corpus luteum, then increases cell secretion and glycogen accumulation, and the stroma dilates with fluid. The glands coil and sacculate. Spiral arteries continue to grow up towards the surface. 3 Helicine arteries rhythmically constrict, then dilate, inducing menstruation or breakdown of the endometrium, altered in the last few days of the secretory phase by a reduction in progesterone level, and by cytokine signals for cellular apoptosis. This sloughing of the functional layer of the endometrium is unaccompanied by blood clotting. 4 Regeneration (physiological) takes place from the basal layer of the endometrium, where the epithelium survives at the bottom of the glands. 5 The mucosa may experience these cyclic changes minimally, even though no oocyte was shed from the Graafian follicle - an anovulatory cycle.

Uterine cervix differs from the corpus thus:

1. It has more collagen and elastic in the wall than muscle.
2. Mucosa is furrowed by complex clefts - plicae palmatae; and does not participate in menstruation.
3. Lining columnar epithelial cells produce a mucus, richly hydrated and penetrable at mid-cycle.
4. Epithelium changes to stratified squamous on the portio vaginalis.
   The boundary between simple columnar and stratified squamous epithelia is unstable, and shifts position by a process of columnar-to-squamous conversion. This transformation zone is prone to dysplasia, then malignant change, which can be detected early by examining 'Pap' smears.

VAGINA	EXTERNAL GENITALIA/VULVA

1 Adventitia of CT, with abundant nerves and blood vessels, merges with some longitudinal and a few circular smooth muscle bundles, around a wide collagenous lamina propria. All these layers loosen in gestation. 2 Epithelium is stratified squamous, rich in glycogen (to promote the growth of benign lactobacilli in the lumen), and influenced by gonadal hormones, but not to the degree seen in rodents. 3 Mucosa has transverse folds or rugae, and may have lymphoid nodules, but is without glands.	1 Labia majora and minora, vestibule and hymen - skin, or stratified squamous epithelium on a loose, fatty or vascular lamina propria. 2 Clitoris and vestibular bulbs - erectile tissue. 3 Sensory receptors are distributed widely in the clitoris, vestibule and labia. 4 Bartholin's glands - mucus-secreting, compound, tubulo-alveolar - are homologues of the male Cowper's glands. Other, minor, vestibular, mucous glands lie near the urethra and clitoris.

25- MAMMARY GLAND/BREAST/MAMMA

	Nipple
1 A collection of compound, tubular (tubulo-alveolar, when active) glands grouped around the 2 nipple, where the lactiferous duct of each gland opens. 3 Glands are in lobes, separated by dense interlobar CT. 4 In each lobe are: (a) a stroma of CT - loose collagenous and adipose tissue, with many lymph and blood vessels; (b) parenchymal tissue of alveoli and ducts, lined with secretory, cuboidal and columnar epithelia. Alveoli and ducts also have myoepithelial cells between epithelium and basal lamina. 5 Lactiferous ducts are lined successively by cuboidal, columnar, stratifed columnar, and stratified squamous epithelia. Each duct widens below the nipple into a sinus.	1 Cornified stratified squamous epithelium covers a stroma of elastic fibres, smooth muscle, and collagen, through which pass the lactiferous ducts. 2 Epithelium is continuous with the somewhat pigmented, glabrous (hairless) epidermis of the surrounded areola, with its sebaceous glands and high dermal papillae. 3 The many autonomic nerve fibres to the nipple's smooth muscle control its rigidity for suckling, and the relaxation of the milk sinuses. 4 Numerous sensory receptors and nerve fibres are present.

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